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(54) Title: METHODS FOR IDENTIFYING AND TREATING RESISTANT TUMORS

(57) Abstract

This invention provides a method of identifying and reversing multidrug resistance in a multidrug resistance tumor comprising administering a multidrug resistance reversing amount of any of the compounds as defined herein.

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Title

METHODS FOR IDENTIFYING AND TREATING RESISTANT TUMORS

Background of the Invention

Along with surgery and radiotherapy, chemotherapy continues to be an effective therapy for many cancers. In fact, several types of cancer are now considered to be curable by chemotherapy and include Hodgkin's disease, large cell lymphoma, acute lymphocytic leukemia, testicular cancer and early stage breast cancer. Other cancers such as ovarian cancer, small cell lung and advanced breast cancer, while not yet curable, are exhibiting positive response to combination chemotherapy.

One of the most important unsolved problems in cancer treatment is drug resistance. Drug resistance includes both intrinsic resistance at the time of treatment using chemotherapy and acquired drug resistance. This problem is a reason for the added importance of combination chemotherapy, as the therapy both has to avoid the emergence of resistant cells and to kill pre-existing cells which are already drug resistant.

Anthracyclines represent an important class of oncolytic agents. Doxorubicin, an anthracycline, which is also known in the art as Adriamycin™, is a drug of choice in the clinical management of breast cancer. Therapy with anthracyclines such as doxorubicin is complicated by the appearance of the anthracycline resistant phenotype which limits or negates the oncolytic activity of doxorubicin.

Topoisomerase inhibitors represent a further class of oncolytic agents. Epipodophyllotoxins such as Etoposide® and Teniposide® are topoisomerase inhibitors which are useful in the therapy of neoplasms of the testis, small-cell lung and other lung, breast, Hodgkin's disease, non-Hodgkin's lymphomas, acute granulocytic leukemia and Karposi's sarcoma. The therapeutic utility of the epipodophylotoxins is limited by the appearance of the epipodophyllotoxin resistant phenotype.

One form of multi-drug resistance (MDR) is mediated by a 170-180 kD energy-dependent efflux pump designated as P-glycoProtein, P-gp. P-gp has been shown to play a major role in the intrinsic and acquired resistance of a number of human tumors against hydrophobic, natural product drugs. Drugs that act as substrates for and are consequently detoxified by P-gp include the vinca alkaloids (vincristine and vinblastine), anthracyclines (Adriamycin), and epipodophyllotoxins (etoposide). While P-gp-associated MDR is a major determinant in tumor cell resistance to chemotherapeutic agents, it is clear that the phenomenon of MDR is multifactorial and involves a number of different mechanisms. One such alternative pathway for resistance to anthracyclines involves the emergence of a 190 kD protein that is not P-gp. *See* McGrath, T., Latoud, C., Arnold, S. T., Safa, A. R., Felsted, R. S., and Center, M. S. Biochem. Pharmacol., **38**: 3611, (1989). P190, also referred to as MRP, is found on the plasma membrane and also appears to be localized in the endoplasmic reticulum *See* Marquardt, D. and Center, M. S., Cancer Res., **52**: 3157, (1992).

MRP possesses a nucleotide binding domain that is homologous with the ATP binding site of P-gp. *See* Marquardt, D., McCrone, S., and Center M. S., Cancer Res., **50**: 1426, (1990). The mechanism(s) utilized by P190 to confer resistance to Adriamycin is not well understood but may involve the intracellular redistribution of Adriamycin away from the nucleus. *See* Marquardt, D. and Center, M. S., *supra*. Adriamycin is an inhibitor of topoisomerase II (Beck,

W. T., Bull. Cancer, 77: 1131, (1990), which is an enzyme involved in DNA replication. Redistribution of Adriamycin away from the nucleus would therefore be an important component in cellular resistance to this drug. The studies published to date on P190 have utilized cell lines selected *in vitro* for resistance to Adriamycin (McGrath, T., Latoud, C., Arnold, S. T., Safa, A. R., Felsted, R. S., and Center, M. S., *supra*; Marquardt, D. and Center, M. S., *supra*; and Marquardt, D., McCrone, S., and Center M. S. Cancer Res., *supra*. The association of MRP (P190) with drug resistance was made by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) of radioactive extracts prepared from Adriamycin-resistant HL60/Adr human leukemia cells labeled with 8-azido-alpha[^{32}P]ATP. *See* McGrath, T., Latoud, C., Arnold, S. T., Safa, A. R., Felsted, R. S., and Center, M. S., *supra*. The drug-resistance phenotype conferred by P190 is not limited to the anthracyclines. Epipodophyllotoxin resistance is linked to P190 expression. The IC_{50}s of HL60/S cells treated with Adriamycin and Etoposide were 0.011 μg/ml and 0.39 μg/ml respectively. The IC_{50}s for HL60/Adr cells (a HL60-derived cell line which is resistant to doxorubicin) treated with Adriamycin and Etoposide were 2.2 μg/ml and >10 μg/ml respectively. HL60/S and HL60/Adr cell lines do not express P-glycoProtein. HL60/Adr expresses P190. Thus, resistance to the anthracyclines and epipodophyllotoxins results from P190 expression.

The present invention embraces the elucidation of the role which MRP plays in multiple drug resistance. MRP functions comprise an energy dependent transporter function to transport a range of oncolytics which include compounds which are generally conjugates of lipophilic compounds having anionic groups such as cysteinyl, carboxyl, cysteinylglycine, glutatione S, glucuronic acid or sulfate groups.

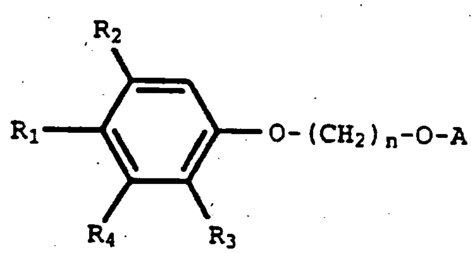
Biochemical characterization of the MRP protein allowed the development of MRP-based assays for compounds which reverse MDR by blocking the transport function of MRP, which

in turn led to the identification of the compounds of the present invention.

SUMMARY OF THE INVENTION

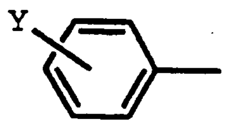
The invention disclosed and claimed herein provides test kits and assay methodology for measuring MRP inhibition as well as compounds and associated formulations for use in reversing multiple drug resistance and therby rendering otherwise refractory neoplasms susceptable to oncolytic therapies. The ability to determine the existance and extent of multiple drug resistance prior to attempts at therapy by evaluating a biopsy sample is a significant advance in the art and allows the elimination of costly and ineffective therapeutic attempts.

Compounds amenable to use in the invention are generally amphiphilic anions having a molecular weight of 300 to 950 and a molecular mass of 300 to 950 daltons respectively. Especially preferred multiple drug resistance compounds for use in accordance with the present invention include: MK571, BAY u9773 and compounds of Formula I:



I

wherein

R_1 is  or CH_3-C(=O)-

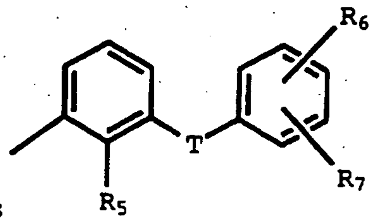
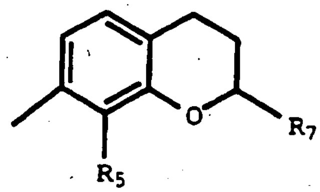
Y is hydrogen or halo;

R_2 is hydrogen, -OH, or $-OCH_3$;

R_3 is C_1-C_6 alkyl;

R_4 is hydrogen, -OH, or $-OCH_3$;

n is 3, 4, or 5;

and A is  or  ;

where

R_5 is hydrogen, C_1-C_6 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, or phenyl;

R_6 is hydrogen or halo;

R_7 is -COOH or 5-tetrazolyl;

T is a bond, $-CH_2-$, -O-, -C(=O)-, or $-S(O)_q-$; and

q is 0, 1, or 2;

provided when one of R_2 and R_4 is -OH or $-OCH_3$, the other of R_2 and R_4 must be hydrogen,

or a pharmaceutically acceptable base addition salt or solvate thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the ATP-dependent transport of [^{3}H]LTC_4 (left-hand) and S-(2,4-dinitrophenyl)-[^{3}H]glutathione (right-hand side) by membrane vesicles of MRP-overexpressing HL60/ADR cells and control cells (cytostatic agent-sensitiv parental cells as well as revertants);

Figure 2 shows [^3H]LTC4-binding proteins and immunoreactive MRP in membranes of HL60/ADR cells (A), revertant HL60 cells (B) and parental, cytostatic agent-sensitive HL60 cells (C). The top illustrates the evidence of MRP by immunoblot, the molecular weights of standard proteins following electrophoretic separation are shown therebelow, and the bottom illustrates the introduction of [^3H]LTC_4 after photoaffinity labeling and separation by SDS polyacrylamide electrophoresis. The suppression of the [^3H]LTC_4 labeling of HL60/ADR membranes by the transport inhibitor MK571 is shown in the left-hand illustration (A).

Figure 3 shows 8-azido[α-^{32}P] ATP-binding proteins in membranes of HL60/ADR cells and revertant, cytostatic agent-sensitive cells.

Figure 4 shows the inhibition of the ATP-dependent transport of LTC_4 by the leukotriene receptor antagonist MK 571. The inhibition is shown in double-reciprocal (Lineweaver and Burk) plot. Membrane vesicles of MRP-overexpressing cells were incubated in the presence of ATP and LTC_4 at 37°C for 2 minutes. Without the inhibitor (O), the transport activity is high, as also shown in Figure 1 (left-hand side). MK 571 (5 micromolar) substantially inhibits transport. The inhibition is competitive. The inhibition constant (K_i) is 0.6 micromolar.

FIGURE 5, Panel A illustrates the ATP-dependent transport of [^3H]etoposide glucuronide into membrane vesicles from MRP-overexpressing cells. Panel B provides a comparison of MRP-mediated ATP-dependent transport of [^3H]etoposide glucuronide and [^3H]etoposide into membrane vesicles from MRP-overexpressing cells. Panel C provides a comparison of MRP-mediated ATP-dependent transport of [^3H]etoposide glucuronide into membrane vesicles from MRP-overexpressing cells and controls cells

and its inhibition by 5 µM MK 571. The structures of etoposide and etoposide glucuronide are provided in Panel D.

FIGURE 6 illustrates the ATP-dependent transport of LTC4 into membrane vesicles from MRP-overexpressing cells and its competitive inhibition by the leukotriene receptor antagonist BAY u9773. The inhibition constant (K_i) is 0.7 micromolar

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have determined that a membrane protein which mediates the ATP-dependent transport of certain conjugates such as glucuronides and glutathione S-conjugates is associated with the cytostatic-agent resistance of certain tumors. The terms cytostatic agent, cytotoxic agent and oncolytic are used interchangeably to describe the present invention and these terms encompass the compounds used in cancer therapy regimens.

Elucidation of the substrate specificity of MRP allowed the selection and characterization of numerous compounds having multiple drug resistance reversal activity. Amphiphilic anions which are lipophilic compounds having a negative charge and a molecular weight of 300 to 950 (daltons), represent substrates for MRP and inhibit its ability to transport cytostatic agents out of the tumor cell again. Of particular interest are compounds which are usually conjugates of lipophilic compounds having anionic groups such as cysteinyl, carboxyl, cysteinylglycine, glutathione S, glucuronic acid or sulfate groups. The glutathione S-conjugate leukotriene C_4 as well as leukotrienes D_4 and E_4 were identified as substrates for the MRP prot in, occurring naturally in the body. For this reason, substances structurally related to the leukotrienes C_4, D_4 and E_4 (LTC_4, LTD_4, LTE_4) are effective inhibitors

for MRP. For example, cysteinyl leukotriene receptor antagonists are in consideration as substances structurally related to the leukotrienes. The receptor antagonists which react with C_4, D_4 and E_4 leukotriene receptors are also understood to include compounds structurally related to the receptor antagonists. The use of these inhibitors leads to an inhibition of MRP and thus to a drastic reduction of the cytostatic-agent resistance in tumors, e.g. in the case of bronchial carcinomas and leukemias. The compounds relevant to the present invention are grouped for description based on the extensive mechanistic data and assay kit development data which was generated using MK 571 and BAY u9773 versus the extensive synthetic chemistry effort directed to the phenoxy compounds of Formula I. Examples 1-18 describe the chemistry and cell-based assay system activity data relevant to the phenoxy compounds of Formula I.

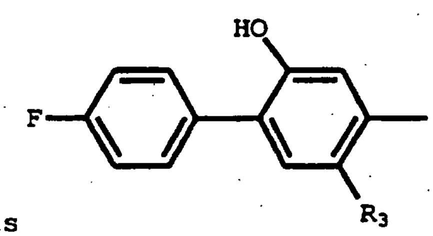
A subset of leukotriene receptor antagonists of particular importance are those described in the scientific and patent literature in association with the bronchodilatation of asthma, e.g. MK 571 and BAY u9773. These compounds and their use in elucidating the mechanism of MRP and assay and kit development are further described below and in Examples 19-21 Results of transporter assays are summarized in Figures 1-6. The studies summarized in Figures 1-6 indicate that the preferred of the inhibitor at the site of action is 0.1 to 10 micromolar. The present inventors have further determined that a concentration of a MDR reversal agent of about 0.5 to to about 50 mg/kg body weight of the patient should be given to achieve the desired concentration at the site of action.

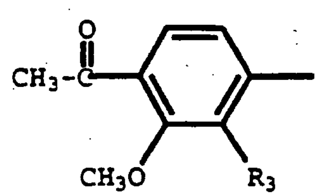
The methodology described in the Examples for evaluating various compounds for their ability to compete with radiolabeled leukotrienes for transport enables the preparation of various kits for measuring transport function or inhibition. Those of ordinary skill in the art will appreciate that various other "detector" groups such

as fluorescent-labeled leukotrienes can be used in lieu of radioisotopes for providing a means to measure leukotriene transport or the inhibition thereof.

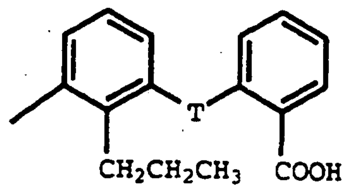
The following definitions refer to the various terms used throughout this disclosure to further describe the compounds of Formula I. The term "C_1-C_6 alkyl" refers to the straight and branched aliphatic radicals of 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, hexyl, and the like. Included within this definition are the terms "C_1-C_3 alkyl", "C_1-C_4 alkyl" and "C_1-C_5 alkyl". The term "C_2-C_5 alkenyl" refers to straight and branched aliphatic radicals of 2 to 5 carbon atoms containing one double bond, such as $-CH=CH_2$, $-CH_2CH=CH_2$, $-CH_2CH_2CH=CH_2$, $-CH_2C(CH_3)=CH_2$, $-CH_2CH=C(CH_3)_2$, and the like. The term "C_2-C_5 alkynyl" refers to straight and branched aliphatic residues of 2 to 5 carbon atoms containing one triple bond, such as $-C\equiv CH$, $-CH_2-C\equiv CH$, $-CH_2CH_2C\equiv CH$, $-CH_2CH(CH_3)C\equiv CH$, $-CH_2C\equiv CCH_3$, and the like. The term "halo" refers to fluoro, chloro, bromo, and iodo.

Preferred compounds of Formula I which are employed in this invention are those wherein R_1 is 4-halo (especially fluoro)phenyl or acetyl. In particular, compounds wherein

R_1-R_4-substituted phenyl is 



or are preferred, especially when R_3 is propyl or ethyl. It is also preferred that R_7 is -COOH and R_5 is either propyl or benzyl. Compounds wh rein

A is  are especially preferred.

This invention includes the use of pharmaceutically acceptable base addition salts of the compounds of Formula I. Such salts include those derived from inorganic bases, such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines, hydroxy alkylamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine, ethanolamine, and the like. The potassium and sodium salt forms are particularly preferred. In addition, this invention includes any solvate forms of the compounds of Formula I or salts thereof, such as ethanol solvates, hydrates, and the like.

It is recognized that in compounds having a branched alkyl functionality, and in those compounds bearing double or triple bonds, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all possible individual isomers and mixtures thereof. The term "5-tetrazolyl" refers to both tautomers, i.e., (1H)-5-tetrazolyl and (2H)-5-tetrazolyl.

An important aspect of the current invention concerns the discovery that a select group of phenoxy compounds, those of Formula I, and the racemate and isomers of MK 571 and Bay u9771 are useful for treating resistant neoplasms. The synthesis of compounds of Formula 1 are taught in Examples 1-18. BAY u977 is commercially avialable from Cascade Biochem LTD, University Park, Whiteknights,

Reading, Berkshire RG6 6BX, United Kingdom. MK571 and structurally related compounds of use in the present invention are taught in US 5,350,761; US 5,260,316; EP 526402-A1; US 5,310,884; US 5,155,130; EP 412,939-A; US 5,120,758; US 5,118,858; US 5,428,171; US 4,851,409; and EP 233763, the entire contents of which are hereby incorporated by reference. The methods of treatment provided by this invention are practiced by administering to a human or other mammal in need a multidrug resistance reversing amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to make the neoplasms less resistant to chemotherapy. In making the neoplasm less resistant, the compounds of the invention may be used on neoplasms having intrinsic and/or acquired resistance. Such neoplasms include those which have a pathway for resistance which includes the protein P190 (MRP). Resistance to drugs such as epipodophyllotoxins and anthracyclines are linked to P190. The treatment of the resistant and susceptible neoplasm will result in a reversal or inhibition of resistance, or in other words, will cause the neoplasm to be more sensitive to the appropriate chemotherapy such as treatment with vinblastine, vincristine, vindesine, navelbine, daunorubicin, doxorubicin, mitroxantrone, etoposide, teniposide, mitomycin C, actinomycin D, taxol, topotecan, mithramycin, colchicine, puromycin, podophyllotoxin, ethidium bromide, emetine, gramicidin D, and valinomycin.

The compounds of the invention may be used for many resistant neoplasms, including colon cancer, mesothelioma, melanoma, prostate cancer, ovarian cancer, non-small cell lung cancer, small-cell lung cancer, bladder cancer, endometrial cancer, leukemia, testicular cancer, breast cancer, and large cell lymphoma. More particular types of cancer are Hodgkin's disease, Karposi's sarcoma, and acute granulocytic leukemia.

Generally, the compound is formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated as elixirs or solutions for convenient oral administration, or administered by the intramuscular or intravenous routes. The compounds can be administered transdermally, and may be formulated as sustained release dosage forms and the like. Formulations containing more than one of the compounds of the present invention are also contemplated for use in the methods of the present invention.

The compounds of Formula I which can be beneficially used in the methods of the current invention can be made according to established procedures, such as those detailed in U.S. Patents No. 5,324,743 and 4,889,871 and EPO Patent Applcation Publication 544,488, all of which are incorporated by reference herein.

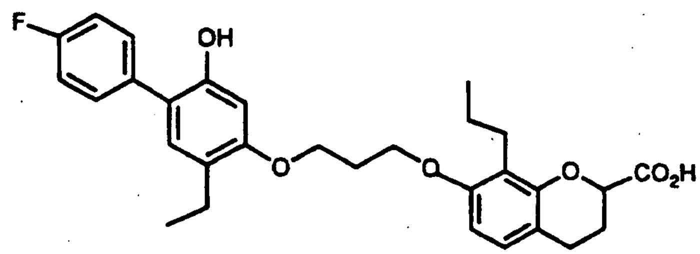
The phenoxy compounds of Formula I employed in this invention are either disclosed in the two aforementioned references or can be prepared according to the same methods as disclosed therein. Other references for preparing other related compounds of this type, generally known as leukotriene antagonists, also provide the skilled organic chemist with methods for preparing such compounds.

The following preparations and examples further illustrate the preparation of the compounds employed in this invention. The examples are illustrative only and are not intended to limit the scope of the invention. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (∂) relative to tetramethylsilane. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free

desorption (FD) conditions, or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. Silica gel chromatography was performed using ethyl acetate/hexane gradients unless otherwise indicated. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water or methanol/water gradient unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted. Where structures were confirmed by infra-red, proton nuclear magnetic resonance, or mass spectral analysis, the compound is so designated by "IR", "NMR", or "MS", respectively.

Example 1

8-Propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid



A. Preparation of ethyl 8-propyl-7-[3-[2-ethyl-4-(4-fluorophenyl)-5-benzyloxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate.

Tetrakis(triphenylphosphine)palladium(0) (0.659 g, 0.6 mmol) and aqueous sodium carbonate solution (20 mL of a 2M solution) were added to a 30 mL benzene solution of ethyl 7-[3-[(2-benzyloxy-1-bromo-5-ethyl-4-yl)oxy]propoxy]-3,4-dihydro-8-propyl-2H-1-benzopyran-2-carboxylate (2.163 g, 3.5 mmol) under an argon atmosphere. The reaction was refluxed for 17 hours, then cooled to room temperature and extracted with ethyl acetate. The organic extract was dried over magnesium sulfate, filtered and the solvent removed under vacuum. The crude product was purified by Waters Prep 500 silica gel chromatography eluting with a gradient of 5% to 20% ethyl acetate/hexane over 50 minutes. The desired title biphenyl was obtained as a clear oil (1.722 g, 78%).

NMR ($CDCl_3$) 7.51 (m, 2), 7.32 (m, 5), 7.09 (m, 3), 6.83 (d, 1, J = 8.32 Hz), 6.62 (s, 1), 6.49 (d, 1, J = 8.50 Hz), 5.02 (s, 2), 4.75 (dd, 1, J = 4.10, 6.50 Hz), 4.22 (m, 6), 2.69 (m, 6), 2.25 (m, 4), 1.59 (m, 2), 1.30 (t, 3, J = 7.10

Hz), 1.21 (t, 3, J = 7.42 Hz), 0.96 (t, 3, J = 7.33 Hz); IR ($CHCl_3$) 3019, 2968, 1745, 1611, 1495 cm^{-1}; Mass Spec. (FAB) (m/z) 627 (M^++1), 626 (M^+), 536.

Analysis for $C_{39}H_{43}O_6$:

Calc:	C,	74.74;	H,	6.91;	F,	3.03;
Found:	C,	74.98;	H,	7.05;	F,	3.39.

B. Preparation of ethyl 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate.

Hydrogen gas was bubbled for 10 minutes through a solution of ethyl 8-propyl-7-[3-[2-ethyl-4-(4-fluorophenyl)-5-benzyloxy-phenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate (1.610 g, 2.57 mmol) in 30 mL of ethyl acetate containing 1.0 g of 10% Pd/C catalyst. The reaction was stirred at room temperature under an atmosphere of hydrogen for 2 hours. The reaction mixture was filtered through a Celite® pad in a sintered glass funnel and the catalyst was washed with ethyl acetate. The solvent was removed from the filtrate providing 1.242 g of a clear oil. The oil was purified by flash chromatography on Merck silica gel eluting with 20% ethyl acetate/hexane. The desired title phenol was obtained in 74% yield (1.020 g) as a white solid.

TLC: Rf = 0.35 (30% ethyl acetate/hexane)
NMR ($CDCl_3$) 7.43 (m, 2), 7.16 (dd, 2, J = 5.97, 5.97 Hz), 6.98 (s,1), 6.82 (d, 1, J = 8.44 Hz), 6.53 (s, 1), 6.46 (d, 1, J = 9.43 Hz), 5.07 (s, 1), 4.76 (m, 1), 4.21 (m, 6), 2.67 (m, 6), 2.26 (m, 4), 1.58 (m, 2), 1.29 (t, 3, J = 6.96 Hz), 1.91 (t, 3, J = 7.35 Hz), 0.96 (t, 3, J = 7.27 Hz); IR (KBr) 3434, 2962, 2869, 1738, 1614, 1588, 1502 cm^{-1}; Mass Spec (FAB) (m/z) 537 (M^++1), 536 (M^+).

Analysis for $C_{32}H_{37}O_6$:

Calc:	C,	71.62;	H,	6.95;
Found:	C,	71.63;	H,	7.06.

C. Preparation of 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid.

A dioxane (12 mL) solution of ethyl 8-propyl-7-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylate (0.968 g, 1.8 mmol) was treated with sodium hydroxide (2.71 mL of a 2N solution) and stirred at room temperature. After 2.5 hours at room temperature, the dioxane was removed from the reaction mixture and the remaining material was diluted with water and acidified to pH 1 with 5N hydrochloric acid. The resulting white milky suspension was then stirred with ethyl acetate and subsequently extracted with ethyl acetate. The organic extract was dried over magnesium sulfate, filtered and the solvent removed to give a white solid (1.098 g). The solid was recrystallized from ethyl acetate/hexane to give the title acid as white needle-like crystals (0.568 g, 62%).

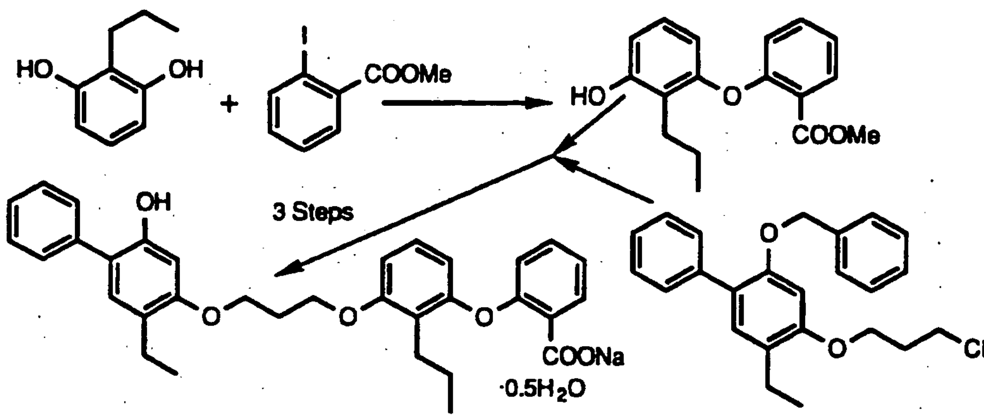
TLC: Rf = 0.31 (10% methanol/methylene chloride)
NMR ($CDCl_3$) ∂ 7.42 (m, 2), 7.15 (dd, 2, J = 8.68), 6.98 (s, 1), 6.85 (d, 1, J = 8.30 Hz), 6.53 (s, 1), 6.52 (d, 1, J = 6.98 Hz), 4.77 (dd, 1, J = 3.63, 7.43 Hz), 4.18 (m, 4), 2.70 (m, 6), 2.27 (m, 4), 1.56 (m, 2), 1.19 (t, 3, J = 7.42 Hz), 0.95 (t, 3, J = 7.30 Hz); IR (KBr) 3421, 2959, 2871, 1706, 1615, 1500 cm^{-1}; Mass Spec (FAB) (m/z) 509 (M^++1), 508 (M^+).

Analysis for $C_{30}H_{33}O_6$:

Calc:	C,	70.78;	H,	6.54;
Found:	C,	70.05;	H,	6.82.

Example 2

2-[2-Propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)-propoxy]phenoxy]benzoic acid sodium salt hemihydrate



A. Preparation of 2-(3-hydroxy-2-propylphenoxy)-benzoic acid methyl ester.

A mixture of 1,3-dihydroxy-2-propylbenzene (75.0 g, 0.490 mol), methyl 2-iodobenzoate (129 g, 0.490 mol), copper bronze (47.0 g, 0.740 mol) and potassium carbonate (81.7 g, 0.592 mol) in dry pyridine (1 L) was thoroughly de-gassed with nitrogen, then refluxed for 6 hours. The mixture was cooled to room temperature, filtered, and concentrated *in vacuo* to reveal a dark sludge. This material was dissolved in ethyl acetate and passed down a short (~ 500 cm^3) Florisil® column. The resulting solution was washed twice with a saturated copper sulfate solution and concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed once with a 0.5 N sodium hydroxide solution, and washed once with a dilute sodium hydroxide solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a cl ar brown oil. Silica gel chromatography (ethyl acetate/hexane) provided 45.4 g (32%) of the desired title intermediate as a white solid: mp 80°C; NMR ($CDCl_3$)

7.92 (dd, J = 7.8, 1.6 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.97 (t, J = 8.1 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 5.65 (bs, 1H, -OH), 3.88 (s, 3H), 2.66 (t, J = 7.6 Hz, 2H), 1.62 (hextet, J = 7.6 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H); MS-FD m/e 286 (p); IR ($CHCl_3$, cm^{-1}) 3350 (b), 2950, 1718, 1602, 1480, 1306, 1255, 1086, 981.

Analysis for $C_{17}H_{18}O_4$:

Calc:	C,	71.31;	H,	6.34;
Found:	C,	71.53;	H,	6.37.

B. Preparation of 2-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid sodium salt hemihydrate.

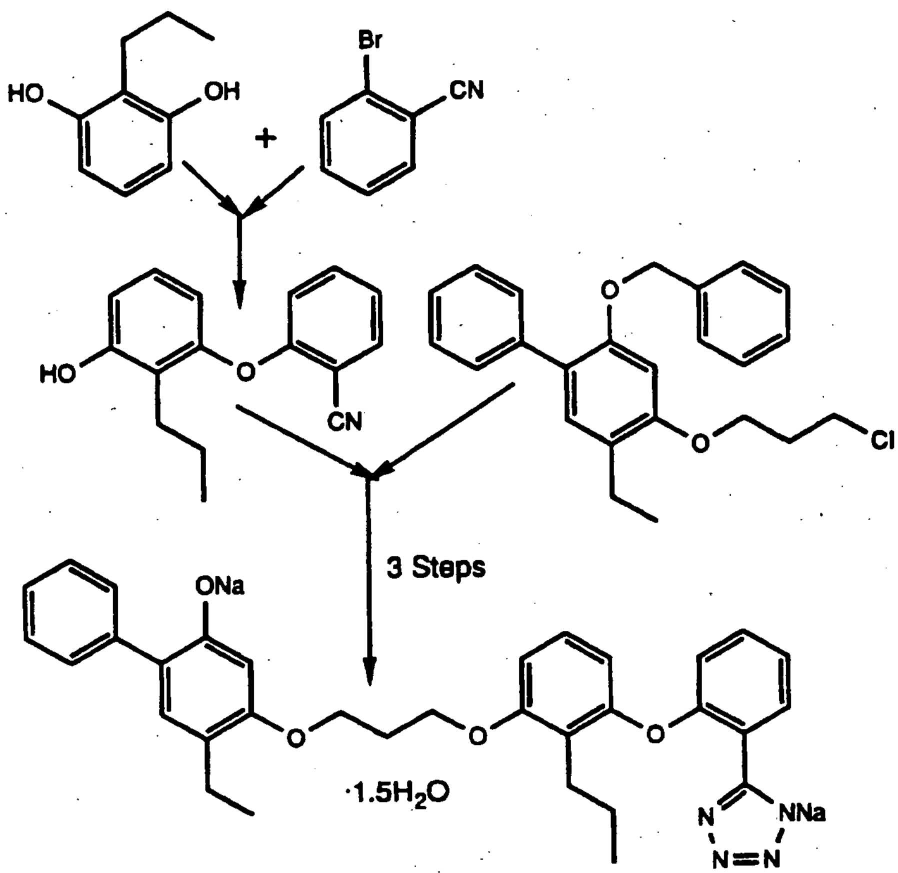
2-(3-Hydroxy-2-propylphenoxy)benzoic acid methyl ester (450 mg, 1.57 mmol) was alkylated with 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene, debenzylated, and hydrolyzed. Salt formation and purification provided 200 mg (21%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 7.48 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.2 Hz, 1H), 7.31 (t, J = 7.4 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.1 Hz, 1H), 6.98 (m, 3H), 6.64 (t, J = 7.2 Hz, 2H), 6.60 (s, 1H), 6.24 (d, J = 7.9 Hz, 1H), 4.15 (m, 2H), 4.02 (m, 2H), 2.61 (m, 2H), 2.49 (m, 2H), 2.16 (t, J = 5.5 Hz, 2H), 1.46 (hextet, J = 6.6 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); MS-FAB m/e 549 (100, p + 1), 526 (32), 295 (28), 252 (34), 227 (20), 213 (21); IR ($CHCl_3$, cm^{-1}) 3450 (b), 2974, 1602, 1586, 1461, 1393, 1240, 1113, 1048.

Analysis for $C_{33}H_{32}O_6Na \cdot 0.5\ H_2O$:

Calc:	C,	71.22;	H,	5.94;
Found:	C,	71.42;	H,	6.16.

Example 3

5-Ethyl-4-[3-[2-propyl-3-[2-(2H-tetrazol-5-yl)phenoxy]phenoxy]propoxy][1,1'-biphenyl]-2-ol disodium salt sesquihydrate



A. Preparation of 3-(2-cyanophenoxy)-2-propylphenol.

A mixture of 3-hydroxy-2-propylphenol (7.50 g, 49.3 mmol), 2-bromobenzonitrile (8.97 g, 49.3 mmol), copper bronze (3.76 g, 59.2 mmol), and potassium carbonate (6.80 g, 49.3 mmol) in pyridine (250 mL) was refluxed for 72 hours. The mixture was cooled to room temperature, filtered, and concentrated *in vacuo*. The residue was

dissolved in ethyl acetat and washed once with water and three times with a saturated copper sulfate solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a dark oil. Silica gel chromatography provided a white solid. Sublimation of this material (bulb-to-bulb distillation apparatus, 200°C) to remove excess 3-hydroxy-2-propylphenol provided 1.79 g (14%) of the desired title intermediate as an off-white crystalline material: mp 103-107°C; NMR ($CDCl_3$) 7.68 (d, J = 8 Hz, 1H), 7.47 (t, J = 7 Hz, 1H), 7.12 (t, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 6.80 (d, J = 9 Hz, 1H), 6.71 (d, J = 9 Hz, 1H), 6.58 (d, J = 9 Hz, 1H), 4.95 (s, 1H, -OH), 2.62 (t, J = 7 Hz, 2H), 1.60 (hextet, J = 6 Hz, 2H), 0.96 (t, J = 7 Hz, 3H); MS-FD m/e 253 (p); IR ($CHCl_3$, cm^{-1}) 3300 (b), 2967, 2234, 1600, 1485, 1483, 1450, 1247, 1097, 980.

Analysis for $C_{16}H_{15}NO_2$:

Calc:	C,	75.87;	H,	5.97;	N,	5.53;
Found:	C,	75.09;	H,	5.88;	N,	5.58.

B. Preparation of 5-ethyl-4-[3-[2-propyl-3-[2-(2H-tetrazol-5-yl)phenoxy]phenoxy]propoxy][1,1'-biphenyl]-2-ol disodium salt sesquihydrate.

3-(2-Cyanophenoxy)-2-propylphenol (1.66 g, 6.56 mmol) was alkylated with 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene. The crude product was dissolved in hexane/ethyl acetate and passed through a short silica gel column. The solution was concentrated *in vacuo* and the residue dissolved in 2-methoxyethanol (50 mL). To this solution was added lithium azide (1.38 g, 24.2 mmol) and triethylammonium bromide (1.30 g, 7.14 mmol). The resulting mixture was refluxed for 48 hours, cooled to room temperature, and passed down a short silica gel column. The column was washed with excess ethyl acetate and the combined washings were concentrated *in vacuo*. The resulting material was de-benzylated and the

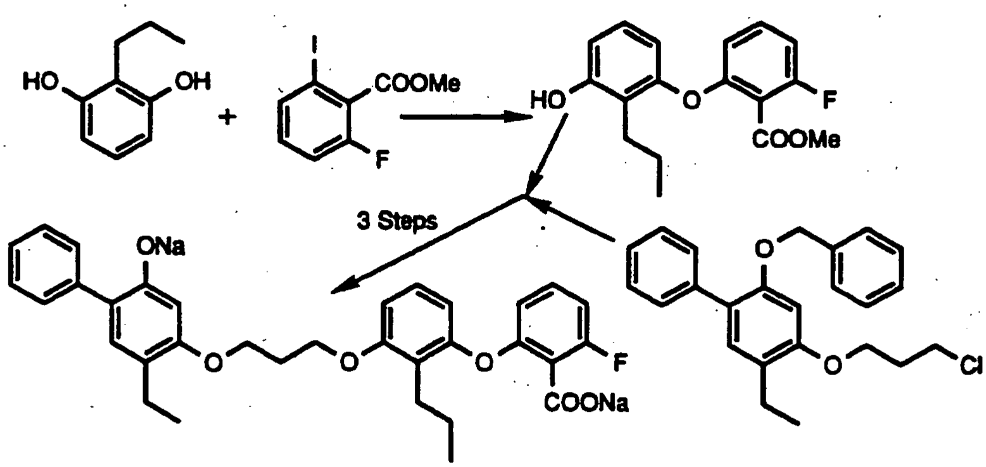
crude tetrazole was converted to the sodium salt and purified to provide 320 mg (8%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 7.81 (dd, J = 7.7, 1.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.21 (m, 2H), 7.11 (t, J = 7.3 Hz, 1H), 6.99 (m, 2H), 6.76 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.56 (s, 1H), 6.22 (d, J = 8.2 Hz, 1H), 4.16 (t, J = 5.8 Hz, 2H), 4.10 (t, J = 5.9 Hz, 2H), 2.61 (t, J = 6.5 H, 2H), 2.48 (m, 2H), 2.22 (m, 2H), 1.45 (hextet, J = 7.4 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.3 Hz, 3H); MS-FAB m/e 595 (35, p + 1), 574 (39), 573 (100), 551(99); IR (KBr, cm^{-1}) 3418 (b), 2962, 1577, 1458, 1243, 1229, 1147, 1117.

Analysis for $C_{33}H_{32}N_4O_4Na_2 \cdot 1.5\ H_2O$:

Calc:	C,	63.76;	H,	5.68;	N,	9.01;
Found:	C,	63.63;	H,	5.59;	N,	8.80.

Example 4

2-Fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid disodium salt



A. Preparation of 2-fluoro-6-(3-hydroxy-2-propyl-phenoxy)benzoic acid methyl ester.

2-Fluoro-6-iodobenzoic acid methyl ester (13.1 g, 46.8 mmol) was submitted to the Ullmann conditions. This procedure provided 3.10 g (22%) of the desired title intermediate as an oil: NMR ($CDCl_3$) 7.26 (m, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.83 (t, J = 8.6 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.53 (d, J = 7.6 Hz, 1H), 5.30 (bs, 1H, -OH), 3.93 (s, 3H), 2.59 (t, J = 7.3 Hz, 2H), 1.56 (hextet, J = 7.6 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H).

B. Preparation of 2-fluoro-6-[2-propyl-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]phenoxy]benzoic acid disodium salt.

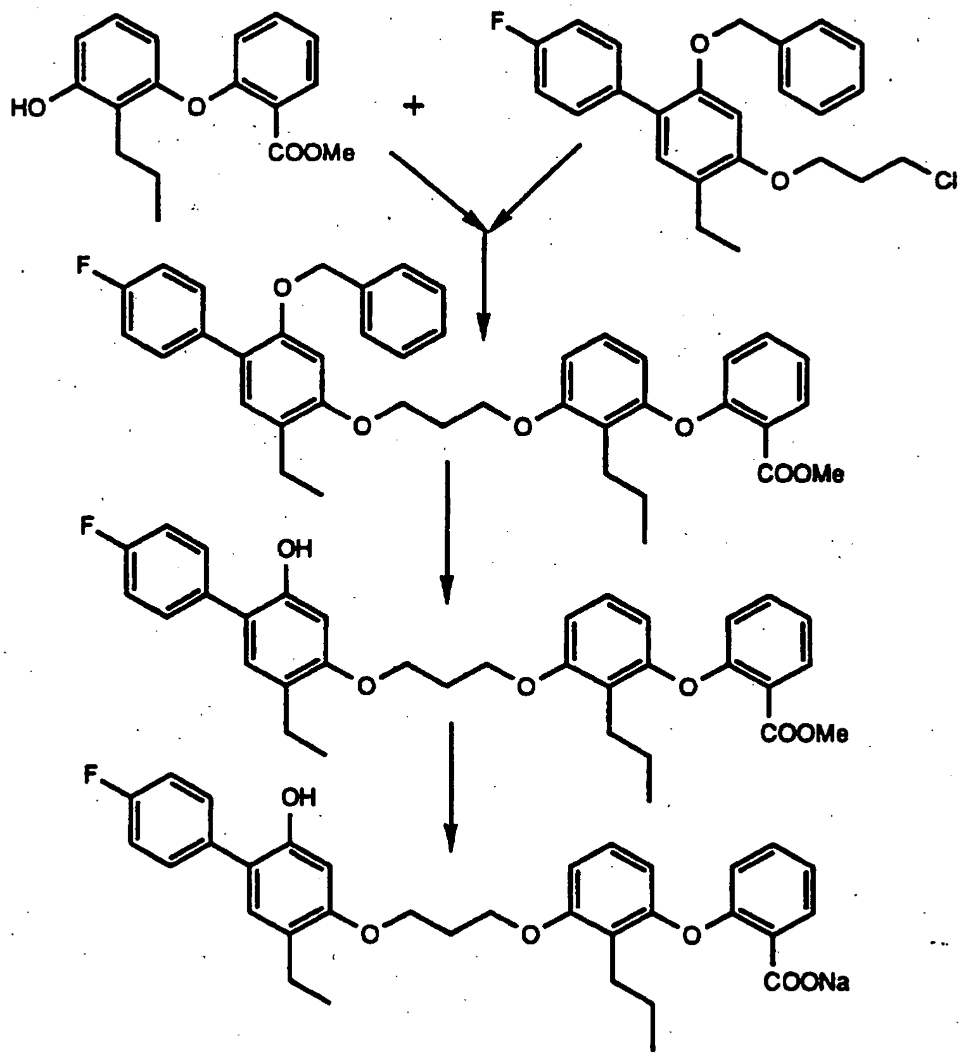
2-Fluoro-6-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (0.660 g, 2.17 mmol) was alkylated with 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene to provide crude product as an oil. The oil was debenzylated, hydrolysed, salified, and purified to provide 468 mg (37%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 7.49 (d, J = 8.8 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.85-7.10 (m, 3H), 6.74 (t, J = 8.1 Hz, 2H), 6.62 (s, 1H), 6.42 (d, J = 8.1 Hz, 1H), 6.33 (d, J = 8.2 Hz, 1H), 4.13 (t, J = 6.0 Hz, 2H), 4.04 (t, J = 5.8 Hz, 2H), 2.40-2.63 (m, 4H), 2.15 (m, 2H), 1.41 (hextet, J = 7.3 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H); MS-FAB m/e 589 (16, p), 568 (36), 567 (100), 546 (30), 527 (15); IR ($CHCl_3$, cm^{-1}) 2975, 1601, 1456, 1395, 1115, 1047.

Analysis for $C_{33}H_{31}O_6FNa_2$:

Calc:	C,	67.34;	H,	5.31;	F,	3.23;
Found:	C,	67.43;	H,	5.59;	F,	2.99.

Example 5

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt



A. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

A mixture of 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene (20.0 g, 50.2 mmol) and

sodium iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was refluxed for 6 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a colorless oil. This material was dissolved in dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (14.4 g, 50.2 mmol) and potassium carbonate (20.8 g, 151 mmol) at room temperature for 24 hours. This mixture was diluted with water and twice extracted with ether. The aqueous layer was separated and back-extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Silica gel chromatography provided 25.4 g (78%) of the desired title intermediate as a pale golden oil: NMR ($CDCl_3$) 7.91 (∂, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.25-7.43 (m, 6H), 7.03-7.38 (m, 5H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 4.24 (t, J = 5.7 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.69 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.34 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 5.0 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); MS-FD m/e 648 (p); IR ($CHCl_3$, cm^{-1}) 2960, 1740, 1604, 1497, 1461, 1112.

Analysis for $C_{41}H_{41}O_6F$:

Calc:	C,	75.91;	H,	6.37;
Found:	C,	76.15;	H,	6.45.

B. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (33.0 g, 50.9 mmol) was de-benzylated to provide 27.3 g (96%) of the title intermediate as an amber oil: NMR

($CDCl_3$) 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (m, 3H), 7.05-7.23 (m, 4H), 6.99 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.05 (s, 1H, -OH), 4.23 (m, 4H), 3.86 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); MS-FD m/e 558 (p); IR ($CHCl_3$, cm^{-1}) 2965, 1727, 1603, 1496, 1458, 1306, 1112.

Analysis for $C_{34}H_{35}O_6F$:

Calc:	C,	73.10;	H,	6.31;
Found:	C,	73.17;	H,	6.42.

C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt.

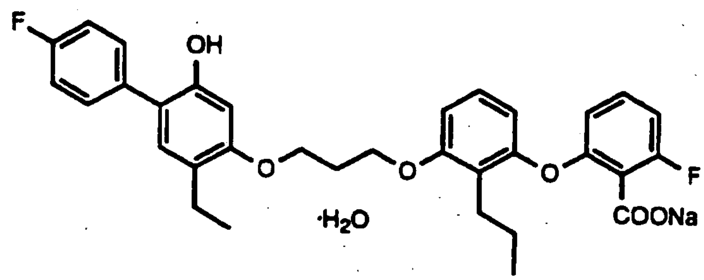
2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (21.5 g, 38.5 mmol) was hydrolyzed. The resulting acid was converted to the sodium salt and purified to provide 16.7 g (77%) of the desired title product as a white amorphous solid: NMR (DMSO-d_6) 10.50 (bs, 1H, -OH), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB m/e 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm^{-1}) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 1112.

Analysis for $C_{33}H_{32}O_6FNa$:

Calc:	C,	69.95;	H,	5.69;	F,	3.35;
Found:	C,	69.97;	H,	5.99;	F,	3.52.

Example 6

2-Fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid disodium salt hydrate



A. Preparation of 2-fluoro-6-[2-propyl-3-[3-[4-bromo-2-ethyl-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

2-Fluoro-6-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (1.84 g, 4.80 mmol) was alkylated with 2-benzyloxy-1-bromo-5-ethyl-4-(3-chloro-1-propyloxy)benzene to provide crude product as an oil. Silica gel chromatography provided 2.05 g (66%) of the purified title intermediate as a colorless oil: NMR ($CDCl_3$) 7.49 (d, J = 7.1 Hz, 2H), 7.20-7.45 (m, 5H), 7.14 (t, J = 8.2 Hz, 1H), 6.82 (t, J = 8.5 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.53 (s, 1H), 6.52 (d, J = 8.5 Hz, 1H), 5.13 (s, 2H), 4.20 (t, J = 6.0 Hz, 2H), 4.13 (t, J = 6.0 Hz, 2H), 3.92 (s, 3H), 2.58 (m, 4H), 2.30 (quintet, J = 6.0 Hz, 2H), 1.51 (hextet, J = 7.6 Hz, 2H), 1.16 (t, J = 7.9 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H).

B. Preparation of 2-fluoro-6-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid disodium salt hydrate.

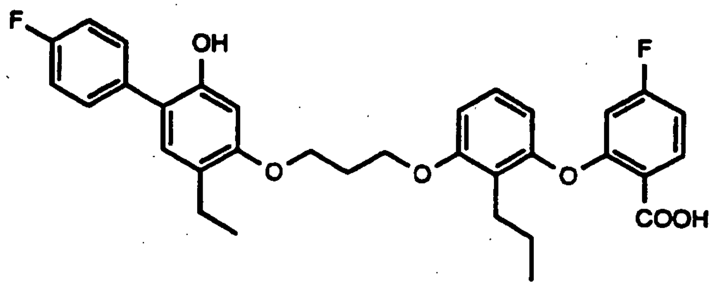
To a solution of 2-fluoro-6-[2-propyl-3-[3-[4-bromo-2-ethyl-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (1.77 g, 2.72 mmol) in benzene (12 mL) was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.30 mmol) and 2.0 M aqueous sodium carbonate (4 mL). To this mixture was added a solution of 4-fluorophenylboronic acid (4.10 g, 8.16 mmol) in ethanol (5 mL). The resulting mixture was refluxed for 4 hours then cooled to room temperature. The mixture was diluted with ethyl acetate and shaken. The organic layer was washed once with water and once with 1N aqueous sodium hydroxide, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide an oil. The product was de-benzylated, hydrolysed, salified, and purified to provide 403 mg (25%) of the desired title product as a fluffy white solid: NMR (DMSO-d_6) 9.83 (bs, 1H), 7.50 (m, 2H), 6.96-7.16 (m, 4H), 6.96 (s, 1H), 6.74 (t, J = 8.4 Hz, 2H), 6.57 (s, 1H), 6.40 (d, J = 8.3 Hz, 1H), 6.35 (d, J = 8.3 Hz, 1H), 4.16 (t, J = 5.7 Hz, 2H), 4.05 (t, J = 5.5 Hz, 2H), 2.40-2.58 (m, 4H), 2.18 (quintet, J = 4.1 Hz, 2H), 1.41 (hextet, J = 7.4 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H); MS-FAB m/e 586 (p + 1, 35), 585 (p, 100), 562 (33), 313 (30). IR ($CHCl_3$, cm^{-1}) 3300 (b), 2967, 1616, 1455, 1398, 1115.

Analysis for $C_{33}H_{31}O_6F_2Na \cdot H_2O$:

Calc:	C,	65.77;	H,	5.52;
Found:	C,	65.81;	H,	5.41.

Example 7

4-Fluoro-2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid



A. Preparation of 4-fluoro-2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester.

To a solution of 2-propylresorcinol (10.0 g, 65.7 mmol) in pyridine (120 mL) was added potassium tert-butoxide (7.00 g, 62.5 mmol) at room temperature with stirring. To this was added a mixture of methyl 2-bromo-4-fluorobenzoate (7.60 g, 32.6 mmol) and copper(I) iodide (12.5 g, 65.7 mmol) in pyridine (120 mL). The resulting mixture was gently refluxed for 4 hours. The reaction was cooled to room temperature and stirred for 18 hours. The mixture was concentrated *in vacuo* and the resulting material dissolved in ethyl ether. The solution was washed once with 5N aqueous hydrochloric acid. The aqueous layer was extracted once with fresh ethyl ether and the combined organic layers were washed twice with 5N aqueous ammonium hydroxide. The organic layer was washed once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography of the resulting residue provided 1.45 g (15%) of the desired intermediate product as a light tan solid: mp 92-94°C; NMR ($CDCl_3$) 7.95 (m, 1H), 7.04 (t, J = 9.5 Hz, 1H), 6.79 (t, J = 9 Hz, 1H), 6.65 (d, J = 9.5 Hz, 1H), 6.50 (m, 2H), 5.25 (bs, 1H, -OH), 3.88 (s, 3H), 2.60

(t, J = 8.7 Hz, 2H), 1.55 (hextet, J = 7.8 Hz, 2H), 0.92 (t, J = 7.8 Hz, 3H); MS-FD m/e 305 (p + 1, 40), 304 (p, 100); IR.

Analysis for $C_{17}H_{17}O_4F$:

Calc:	C,	67.10;	H,	5.63;
Found:	C,	67.32;	H,	5.78.

B. Preparation of 4-fluoro-2-[2-propyl-3-[3-[4-(4-fluorophenyl)-2-ethyl-5-(phenylmethoxy)phenoxy]propoxy]-phenoxy]benzoic acid methyl ester.

4-Fluoro-6-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (0.534 g, 1.75 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene to provide crude product as an oil. Purification via silica gel chromatography provided 640 mg (55%) of the desired title intermediate as a white crystalline solid: mp 77-78°C; NMR ($CDCl_3$) 7.95 (t, J = 7.8 Hz, 1H), 7.53 (m, 2H), 7.32 (m, 4H), 7.03-7.20 (m, 3H), 6.77 (m, 2H), 6.62 (s, 1H), 6.55 (d, J = 8 Hz, 1H), 6.50 (d, J = 9 Hz, 1H), 5.05 (s, 2H), 4.25 (m, 4H), 3.89 (s, 3H), 2.65 (m, 4H), 2.34 (quintet, J = 6 Hz, 4H), 1.55 (hextet, J = 6 Hz, 2H), 1.22 (t, J = 7 Hz, 3H), 0.92 (t, J = 7 Hz, 3H); MS-FD m/e 666 (p); IR ($CHCl_3$, cm^{-1}) 2960, 1730, 1600, 1499, 1461, 1268, 1110.

Analysis for $C_{44}H_{40}O_6F_2$:

Calc:	C,	73.86;	H,	6.05;
Found:	C,	73.17;	H,	6.44.

C. Preparation of 4-fluoro-2-[2-propyl-3-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

4-Fluoro-2-[2-propyl-3-[3-[4-(4-fluorophenyl)-2-ethyl-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (590 mg) was dissolved in ethyl acetate (25 mL) containing 10% palladium on carbon (118 mg) and

hydrogenated at 2 atmospheres for 18 hours. The mixture was filtered through Celite® and concentrated *in vacuo* to provide an oil. Purification of the crude material via silica gel chromatography provided 400 mg (79%) of the title intermediate as a glass: NMR ($CDCl_3$) 7.97 (t, J = 7.8 Hz, 1H), 7.44 (m, 2H), 7.17 (m, 3H), 7.03 (s, 1H), 6.79 (m, 2H), 6.45-6.63 (m, 3H), 5.38 (bs, 1H, -OH), 4.22 (m, 4H), 3.92 (s, 3H), 2.65 (m, 4H), 2.35 (quintet, J = 5 Hz, 2H), 1.57 (hextet, J = 7 Hz, 2H), 1.24 (t, J = 7.8 Hz, 3H), 0.95 (t, J = 7.8 Hz, 3H); MS-FD m/e 578 (p + 2, 50), 577 (p + 1, 90), 576 (p, 100); IR ($CHCl_3$, cm^{-1}) 3563 (b), 2965, 1722, 1604, 1585, 1497, 1461, 1267, 1251, 1152, 1110.

Analysis for $C_{34}H_{34}O_6F_2$:

Calc:	C,	70.82;	H,	5.94;
Found:	C,	71.12;	H,	5.96.

D. Preparation of 4-fluoro-2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]-phenoxy]benzoic acid.

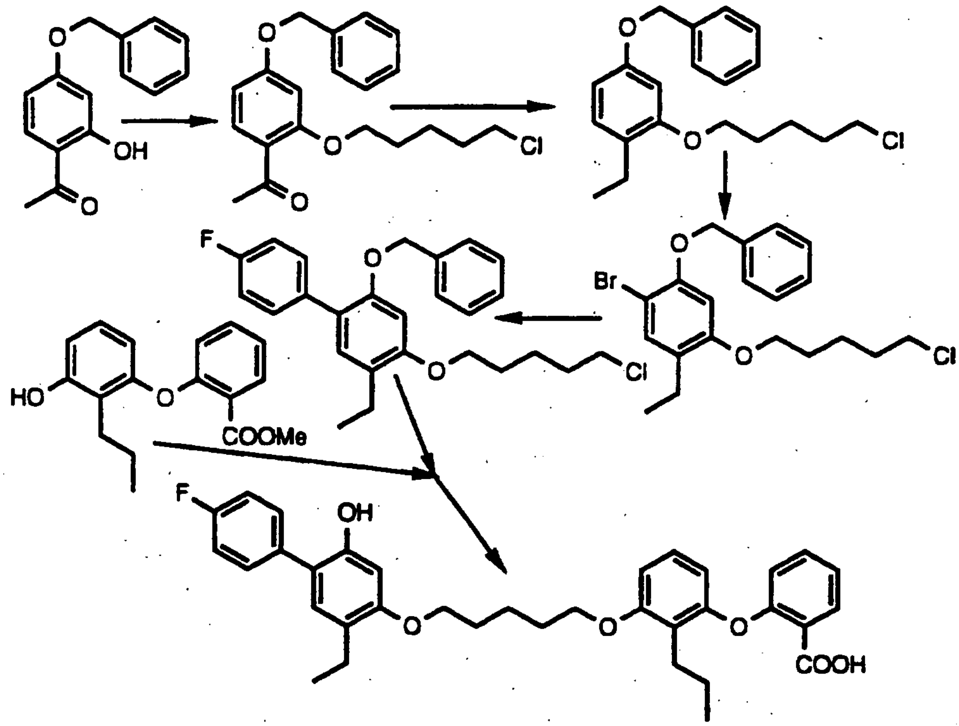
4-Fluoro-2-[2-propyl-3-[3-[4-(4-fluorophenyl)-2-ethyl-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (350 mg) was hydrolyzed to provide 310 mg (91%) of the desired title product as a white solid: mp 62-64°C; NMR ($CDCl_3$) 8.21 (t, J = 7.8 Hz, 1H), 7.35 (m, 2H), 7.10-7.30 (m, 3H), 7.97 (s, 1H), 6.84 (m, 2H), 6.63 (d, J = 6.8 Hz, 1H), 6.52 (s, 1H), 6.41 (d, J = 9 Hz, 1H), 5.10 (bs, 1H, -OH), 4.23 (m, 4H), 2.57 (m, 4H), 2.34 (quintet, J = 5 Hz, 2H), 1.50 (hextet, J = 6 Hz, 2H), 1.17 (t, J = 7.8 Hz, 3H), 0.88 (t, = 7.8 Hz, 3H); MS-FD m/e 564 (p + 2, 30), 562 (p, 100); IR ($CHCl_3$, cm^{-1}) 3379 (b), 2963, 1699, 1607, 1500, 1268, 1247, 1146, 1110, 839.

Analysis for $C_{33}H_{32}O_6F_2$:

Calc:	C,	70.45;	H,	5.73;
Found:	C,	70.15;	H,	5.81.

Example 8

2-[2-Propyl-3-[5-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic acid



A. Preparation of 2-(5-chloropentoxy)-4-(phenylmethoxy)acetophenone.

A mixture of 2-hydroxy-4-(phenylmethoxy)acetophenone (15.5 g, 64.0 mmol), potassium carbonate (8.83 g, 64.0 mmol), and dimethylsulfoxide (15 mL) in 2-butanone (145 mL) was stirred at room temperature for 30 minutes. 1-Bromo-5-chloropentane (11.9 g, 64.0 mmol) was added and the resulting mixture heated at reflux for 18 hours. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a waxy solid. Purification via silica gel

chromatography (ethyl acetate/hexane) provided 16.1 g (73%) of the title intermediate as a white solid: mp 76-77°C; NMR ($CDCl_3$) 7.85 (d, J = 8.7 Hz, 1H), 7.43 (m, 5H), 6.59 (d, J = 8.5 Hz, 1H), 6.53 (s, 1H), 5.11 (s, 2H), 4.05 (t, J = 6 Hz, 2H), 3.61 (t, J = 6 Hz, 2H), 2.60 (s, 3H), 1.90 (m, 4H), 1.69 (m, 2H); MS-FD m/e 348 (p + 2, 65), 346 (p, 100); IR ($CHCl_3$, cm^{-1}) 3025, 1662, 1598, 1268, 1184, 1139, 1027.

B. Preparation of 2-(5-chloropentoxy)-4-(phenylmethoxy)ethylbenzene.

To a solution of 2-(5-chloropentoxy)-4-(phenylmethoxy)-acetophenone (15.0 g, 43.2 mmol) in trifluoroacetic acid (33.3 mL) at 0°C was added triethylsilane (11.0 g, 95.1 mmol) dropwise. The resulting mixture was stirred at 0°C for 2.5 hours then treated with excess saturated sodium bicarbonate solution. The mixture was extracted with ether. The organic layer was washed once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to reveal a yellow oil. Purification via silica gel chromatography (ethyl acetate/hexane) provided 10.45 g (73%) of the title intermediate as a faint yellow oil: NMR ($CDCl_3$) 7.20-7.55 (m, 5H), 7.08 (d, J = 9.7 Hz, 1H), 6.53 (s, 1H), 6.51 (d, J = 8.7 Hz, 1H), 5.05 (s, 2H), 3.95 (t, J = 6.8 Hz, 2H), 3.60 (t, J = 6.8 Hz, 2H), 2.59 (q, J = 7.8 Hz, 2H), 1.75-1.95 (m, 4H), 1.69 (quintet, J = 6 Hz), 1.18 (t, J = 7.8 Hz, 3H); MS-FD m/e ; IR ($CHCl_3$, cm^{-1}) 2937, 1613, 1587, 1505, 1289, 1258, 1172, 1132, 1028.

Analysis for $C_{20}H_{25}O_2Cl$:

Calc:	C,	72.12;	H,	7.57;
Found:	C,	71.24;	H,	7.64.

C. Preparation of 3-bromo-6-(5-chloropentoxy)-4-(phenylmethoxy)ethylbenzene.

A mixture of 2-(5-chloropentoxy)-4-(phenylmethoxy)-ethylbenzene (10.0 g, 31.0 mmol) and N-bromosuccinimide (5.35 g, 30.1 mmol) in carbon tetrachloride (100 mL) was warmed slightly for 2 hours, then stirred at room temperature for 18 hours. The mixture was washed sequentially with water, 1N aqueous sodium thiosulfate solution, and saturated sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a white solid. Recrystallization from hexane provided 10.0 g (81%) of the desired title intermediate as a white crystalline solid: mp 54-55°C; NMR ($CDCl_3$) 7.50 (m, 2H), 7.25-7.48 (m, 4H), 6.48 (s, 1H), 5.15 (s, 2H), 3.91 (t, J = 6 Hz, 2H), 3.58 (t, J = 6 Hz, 2H), 2.55 (q, J = 7 Hz, 2H), 1.85 (m, 4H), 1.65 (m, 2H), 1.16 (t, J = 7.8 Hz, 3H); MS-FD m/e 414 (p + 2, 25), 412 (p, 100), 410 (p - 2, 85); IR ($CHCl_3$, cm^{-1}) 2950, 1602, 1501, 1450, 1370, 1300, 1163.

Analysis for $C_{20}H_{24}O_2BrCl$:

Calc:	C,	58.34;	H,	5.87;
Found:	C,	58.31;	H,	6.04.

D. Preparation of 6-(5-chloropentoxy)-2-(4-fluorophenyl)-4-(phenylmethoxy)ethylbenzene.

3-Bromo-6-(5-chloropentoxy)-4-(phenylmethoxy)-ethylbenzene (8.80 g, 26.4 mmol) was coupled to 4-fluorophenyl-boronic acid. Purification via silica gel chromatography (ethyl acetate/hexane) followed by recrystallization from hexane provided 7.04 g (77%) of the intermediate title product as a white solid: mp 55-56°C; NMR ($CDCl_3$) 7.54 (m, 2H), 7.33 (m, 5H), 7.11 (m, 3H), 6.59 (s, 1H), 5.07 (s, 2H), 3.99 (t, J = 6 Hz, 2H), 3.62 (t, J = 6 Hz, 2H), 2.65 (q, J = 8 Hz, 2H), 1.90 (m, 4H), 1.70 (m, 2H), 1.14 (t, J = 8 Hz, 3H); IR ($CHCl_3$, cm^{-1}) 2938, 1613, 1497, 1143, 1027.

Analysis for $C_{26}H_{28}O_2ClF$:

Calc:	C,	73.14;	H,	6.61;
Found:	C,	72.91;	H,	6.69.

E. Preparation of 2-[2-propyl-3-[5-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]pentoxy]phenoxy]-benzoic acid methyl ester.

2-(3-Hydroxy-2-propylphenoxy)benzoic acid methyl ester (2.00 g, 6.99 mmol) was alkylated with 6-(5-chloropentoxy)-2-(4-fluorophenyl)-4-(phenylmethoxy)ethylbenzene to provide crude product as an oil. Purification via silica gel chromatography (ethyl acetate/hexane) provided 3.90 g (83%) of title intermediate as a colorless oil: NMR ($CDCl_3$) 7.94 (d, J = 8 Hz, 1H), 7.55 (m, 2H), 7.35 (m, 6H), 7.11 (m, 5H), 6.85 (d, J = 9 Hz, 1H), 6.70 (d, J = 9 Hz, 1H), 6.60 (s, 1H), 6.48 (d, J = 9 Hz, 1H), 5.07 (s, 2H), 4.08 (t, J = 5 Hz, 2H), 4.03 (t, J = 5 Hz, 2H), 3.89 (s, 3H), 2.70 (m, 4H), 1.95 (m, 4H), 1.76 (m, 2H), 1.62 (m, 2H), 1.24 (t, J = 7 Hz, 3H), 0.95 (t, J = 7 Hz, 3H); MS-FD m/e 677 (p + 1, 65), 676 (p, 100); IR ($CHCl_3$, cm^{-1}) 2965, 1740, 1604, 1497, 1461, 1453, 1306, 1111.

Analysis for $C_{42}H_{45}O_6F$:

Calc:	C,	76.31;	H,	6.70;
Found:	C,	76.24;	H,	6.83.

F. Preparation of 2-[2-propyl-3-[5-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]pentoxy]phenoxy]benzoic acid.

2-[2-Propyl-3-[5-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]pentoxy]phenoxy]benzoic acid methyl ester (3.60 g, 5.32 mmol) was submitted to de-benzylation and hydrolysis. The resulting product was isolated via vacuum filtration as a white crystalline solid: mp 65°C (dec); NMR ($CDCl_3$) 8.25 (dd, J = 7.9, 1.7 Hz, 1H), 7.44 (m,

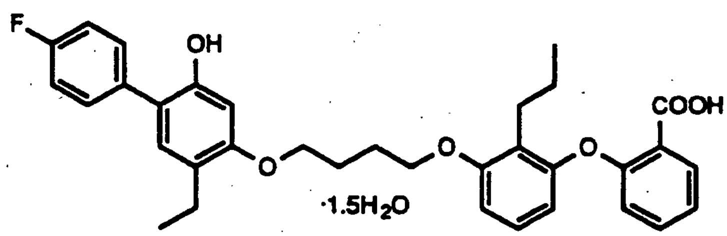
3H), 7.18 (m, 4H), 6.97 (s, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.54 (s, 1H), 5.15 (bs, 1H, -OH), 4.10 (t, J = 6.1 Hz, 2H), 4.05 (t, J = 5.6 Hz, 2H), 2.61 (m, 4H), 1.93 (m, 4H), 1.75 (m, 2H), 1.54 (hextet, J = 7.4 Hz, 2H), 1.18 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H); MS-FD m/e 572 (p); IR ($CHCl_3$, cm^{-1}) 3350 (b), 2965, 1739, 1605, 1496, 1455, 1238, 1108.

Analysis for $C_{35}H_{37}O_6F$:

Calc:	C,	73.41;	H,	6.51;
Found:	C,	73.13;	H,	6.59.

Example 9

2-[2-Propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]butoxy]phenoxy]benzoic acid sesquihydrate



A. Preparation of 2-(4-chlorobutoxy)-4-(phenylmethoxy)acetophenone.

2-Hydroxy-4-(phenylmethoxy)acetophenone (9.20 g, 37.9 mmol) was alkylated with 1-bromo-4-chlorobutane. The crude material was purified via silica gel chromatography (ethyl acetate/hexane) to provide 7.70 g (61%) of the desired title product as a white solid: mp 58-60°C; NMR ($CDCl_3$) 7.83 (d, J = 9 Hz, 1H), 7.33-7.47 (m, 5H), 6.59 (dd, J = 9, 2 Hz, 1H), 6.53 (d, J = 2 Hz, 1H), 5.10 (s, 2H), 4.05 (t, J = 5 Hz, 2H), 3.62 (t, J = 5 Hz, 2H), 2.57 (s, 3H), 2.02 (m, 4H); MS-FD m/e 334 (p + 1, 50), 333 (p, 28), 332 (p - 1, 100); IR ($CHCl_3$, cm^{-1}) 3013, 1663, 1599, 1267, 1184, 1027.

Analysis for $C_{19}H_{21}O_3Cl$:

Calc:	C,	68.57;	H,	6.36;
Found:	C,	68.77;	H,	6.60.

B. Preparation of 2-(4-chlorobutoxy)-4-(phenylmethoxy)ethylbenzene.

2-(4-Chlorobutoxy)-4-(phenylmethoxy)-acetophenone (3.50 g, 10.5 mmol) was reduced. Purification via silica gel chromatography (ethyl acetate/hexane) provided 2.60 g (79%) of the desired title intermediate as a colorless oil: NMR ($CDCl_3$) 7.13-7.55 (m, 5H), 7.08 (d, J = 8.9 Hz, 1H), 6.54 (m, 2H), 5.07 (s, 2H), 3.99 (d, J = 5.7 Hz, 2H), 3.65 (t, J = 6.0 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.00 (m, 4H), 1.22 (t, J = 7.5 Hz, 3H); MS-FD m/e; IR ($CHCl_3$, cm^{-1}) 2966, 1613, 1506, 1289, 1171, 1132, 1028.

Analysis for $C_{19}H_{23}O_2Cl$:

Calc:	C,	71.57;	H,	7.27;
Found:	C,	71.78;	H,	7.40.

C. Preparation of 3-bromo-6-(4-chlorobutoxy)-4-(phenylmethoxy)ethylbenzene.

2-(4-Chlorobutoxy)-4-(phenylmethoxy)ethylbenzene (2.50 g, 7.84 mmol) was brominated. Recrystallization of the crude product from hexane provided 2.52 g (81%) of the desired title product: mp 65-66°C; NMR ($CDCl_3$) 7.50 (d, J = 8 Hz, 2H), 7.34-7.48 (m, 3H), 7.32 (s, 1H), 6.49 (s, 1H), 5.15 (s, 2H), 3.92 (t, J = 5.6 Hz, 2H), 3.64 (t, J = 5.9 Hz, 2H), 2.55 (q, J = 7.5 Hz, 2H), 1.97 (m, 4H), 1.15 (t, J = 7.5 Hz, 3H); MS-FD m/e 398 (p, 100), 396 (p - 2, 70); IR ($CHCl_3$, cm^{-1}) 2967, 1602, 1501, 1455, 1389, 1285, 1163, 1060.

Analysis for $C_{19}H_{22}O_2BrCl$:

Calc:	C,	57.38;	H,	5.57;
Found:	C,	57.27;	H,	5.62.

D. Preparation of 6-(4-chlorobutoxy)-2-(4-fluorophenyl)-4-(phenylmethoxy)ethylbenzene.

3-Bromo-6-(4-chlorobutoxy)-4-(phenylmethoxy)-ethylbenzene (2.30 g, 26.4 mmol) was coupled to 4-fluorophenylboronic acid. Purification via silica gel chromatography (ethyl acetate/hexane) followed by trituration with methanol provided 2.07 g (87%) of the titled intermediate product as a white solid: mp 48-49°C; NMR ($CDCl_3$) 7.55 (m, 2H), 7.35 (m, 5H), 7.12 (m, 3H), 6.59 (s, 1H), 5.08 (s, 2H), 4.03 (t, J = 5.3 Hz, 2H), 3.68 (t, J = 5.3 Hz, 2H), 2.67 (q, J = 7.5 Hz, 2H), 2.02 (m, 4H), 1.24 (t, J = 7.5 Hz, 3H); MS-FD m/e 412 (p); IR.

Analysis for $C_{25}H_{26}O_2ClF$:

Calc:	C,	72.72;	H,	6.35;
Found:	C,	72.59;	H,	6.46.

E. Preparation of 2-[2-propyl-3-[4-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]butoxy]phenoxy]-benzoic acid methyl ester.

2-(3-Hydroxy-2-propylphenoxy)benzoic acid methyl ester (1.40 g, 4.84 mmol) was alkylated with 6-(4-chlorobutoxy)-2-(4-fluorophenyl)-4-(phenylmethoxy)ethylbenzene to provide crude product as an oil. Purification via silica gel chromatography (ethyl acetate/hexane) provided 2.40 g (75%) of the title intermediate as a colorless oil: NMR ($CDCl_3$) 7.93 (dd, J = 6.2, 1.7 Hz, 1H), 7.54 (m, 2H), 7.25-7.45 (m, 6H), 7.13 (m, 5H), 6.88 (d, J = 8.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 6.63 (s, 1H), 6.50 (d, J = 8.3 Hz, 1H), 5.07 (s, 2H), 4.12 (m, 4H), 3.89 (s, 3H), 2.68 (m, 4H), 2.09 (m, 4H), 1.63 (hextet, J = 7.4 Hz, 2H), 1.15 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); MS-FD m/e 663 (p + 1, 35), 662 (p, 100); IR ($CHCl_3$, cm^{-1}) 3470, 2950, 1760, 1740, 1461, 1305, 1135, 1071.

Analysis for $C_{42}H_{43}O_6F$:

Calc:	C,	76.11;	H,	6.54;
Found:	C,	76.36;	H,	6.65.

F. Preparation of 2-[2-propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]butoxy]phenoxy]benzoic acid sesquihydrate.

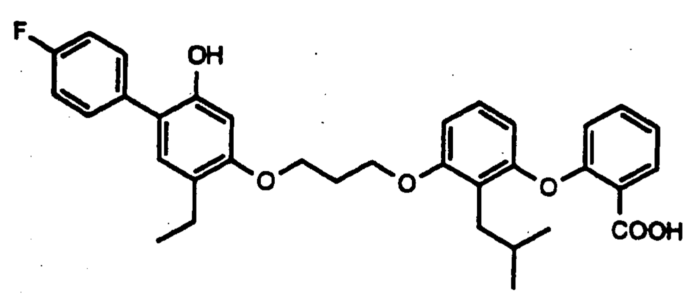
2-[2-Propyl-3-[4-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]butoxy]phenoxy]benzoic acid methyl ester (2.20 g, 3.32 mmol) was submitted to de-benzylation and hydrolysis. This procedure provided 1.00 g (85%) of the title product as a white solid: mp 65-68°C; NMR ($CDCl_3$) 8.26 (dd, J = 6.0, 1.8 Hz, 1H), 7.43 (m, 3H), 7.12-7.29 (m, 4H), 6.99 (s, 1H), 6.81 (d, J = 8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8 Hz, 1H), 6.53 (s, 1H), 5.08 (bs, 1H, -OH), 4.12 (m, 4H), 2.63 (m, 4H), 2.08 (m, 4H), 1.55 (hextet, J = 7.4 Hz, 2H), 1.20 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H); MS-FD m/e 559 (p + 1, 57), 558 (p, 100); IR ($CHCl_3$, cm^{-1}) 3350 (b), 2950, 1739, 1625, 1496, 1455, 1237, 1108.

Analysis for $C_{34}H_{35}O_6F \cdot 1.5\ H_2O$:

Calc:	C,	69.73;	H,	6.43;
Found:	C,	69.74;	H,	6.54.

Example 10

2-[2-(2-Methylpropyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid



A. Preparation of 2-(2-methylpropyl)-1,3-dimethoxybenzene.

To a solution of 1,3-dimethoxybenzene (38.0 g, 272 mmol) in tetrahydrofuran (380 mL) at 0°C was added a 1.6M solution of butyllithium in hexane (188 mL, 299 mmol). The resulting mixture was stirred at 0°C for 2 hours. 1-Iodo-2-methylpropane (50.0 g, 272 mmol) was added and the reaction mixture warmed to room temperature, then refluxed for 36 hours. The mixture was cooled to room temperature, diluted with saturated ammonium chloride solution, and extracted twice with ethyl acetate. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica chromatography (ethyl acetate/hexane) provided 13.8 g (26%) of title intermediate product as a colorless oil: NMR ($CDCl_3$) 7.22 (t, J = 9 Hz, 1H), 6.33 (d, J = 10 Hz, 2H), 3.89 (s, 6H), 2.66 (d, J = 9 Hz, 2H), 2.03 (heptet, J = 8 Hz, 1H), 1.00 (d, J = 8 Hz, 6H); IR ($CHCl_3$, cm^{-1}) 2959, 1593, 1474, 1261, 1133, 1075.

B. Preparation of 2-(2-methylpropyl)-1,3-dihydroxybenzene.

2-(2-Methylpropyl)-1,3-dimethoxybenzene (18.0 g, 92.8 mmol) was melted with pyridinium hydrochloride (90 g) and stirred at 180°C for 8 hours. The mixture was cooled to room temperature, diluted with water, and extracted twice with ethyl acetate. The organic phase was washed with dilute aqueous hydrochloric acid, dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification via silica gel chromatography (ether/hexane) provided 15.0 g (98%) of title intermediate as a light yellow oil: NMR ($CDCl_3$) 6.97 (t, J = 9 Hz, 1H), 6.43 (d, J = 10 Hz, 2H), 5.68 (s, 2H, -OH), 2.59 (d, J = 9 Hz, 2H), 2.03 (heptet,

J = 8 Hz, 1H), 1.00 (d, J = 8 Hz, 6H); MS-FD m/e 166 (p); IR ($CHCl_3$, cm^{-1}) 3603, 3349 (b), 2959, 1601, 1466, 1298, 1104, 987.

Analysis for $C_{10}H_{14}O_2$:

Calc:	C,	72.26;	H,	8.49;
Found:	C,	72.37;	H,	8.75.

C. Preparation of 2-[3-hydroxy-2-(2-methylpropyl)-phenoxy]benzoic acid methyl ester.

2-(2-Methylpropyl)-1,3-dihydroxybenzene (14.5 g, 87.3 mmol) was submitted to Ullmann coupling conditions with methyl 2-iodobenzoate. Purification of the crude product via silica gel chromatography (ether/hexane) provided 3.11 g (12%) of the desired title intermediate as a light yellow oil: NMR ($CDCl_3$) 7.91 (d, J = 8 Hz, 1H), 7.23 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 6.99 (t, J = 8 Hz, 1H), 6.86 (d, J = 9 Hz, 1H), 6.63 (d, J = 9 Hz, 1H), 6.39 (d, J = 9 Hz, 1H), 5.42 (bs, 1H, -OH), 3.84 (s, 3H), 2.58 (d, J = 9 Hz, 2H), 2.08 (heptet, J = 8 Hz, 1H), 0.99 (d, J = 8 Hz, 6H); MS-FD m/e 300 (p); IR ($CHCl_3$, cm^{-1}) 3625, 3360 (b), 2950, 1718, 1602, 1453, 1306, 1235, 1107, 910.

Analysis for $C_{18}H_{20}O_4$:

Calc:	C,	71.98;	H,	6.71;
Found:	C,	72.19;	H,	6.86.

D. Preparation of 2-[2-(2-methylpropyl)-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]-phenoxy]benzoic acid methyl ester.

2-[3-Hydroxy-2-(2-methylpropyl)phenoxy]benzoic acid methyl ester (750 mg, 2.51 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene to provide crude product as an oil. Purification via silica gel chromatography (ether/hexane) provided 620 mg (35%) of title intermediate product as an off-white solid: mp 82-84°C; NMR ($CDCl_3$) 7.99 (d, J = 8

Hz, 1H), 7.62 (t, J = 7 Hz, 2H), 7.38 (m, 6H), 7.18 (m, 5H), 6.90 (d, J = 9H, 1H), 6.78 (d, J = 9 Hz, 1H), 6.71 (s, 1H), 6.53 (d, J = 9 Hz, 1H), 5.09 (s, 2H), 4.27 (m, 4H), 3.91 (s, 3H), 2.70 (m, 4H), 2.39 (quintet, J = 8 Hz, 2H), 2.10 (heptet, J = 8 Hz, 1H), 1.30 (t, J = 9 Hz, 3H), 1.00 (d, J = 8 Hz, 6H); MS-FD m/e 663 (p + 1, 42), 662 (p, 100); IR (KBr, cm^{-1}) 3425 (b), 2959, 2864, 1733, 1604, 1580, 1500, 1447, 1246, 1080, 837.

Analysis for $C_{42}H_{43}O_6F$:

Calc:	C,	76.11;	H,	6.54;
Found:	C,	76.20;	H,	6.83.

E. Preparation of 2-[2-(2-methylpropyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid.

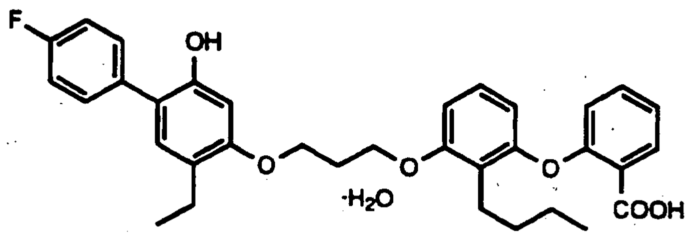
2-[2-(2-Methylpropyl)-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (600 mg, 0.906 mmol) was submitted to debenzylation conditions. Hydrolysis of the resulting ester provided 250 mg (57%) of title product as an off-white solid: mp 48-49°C; NMR ($CDCl_3$) 8.25 (d, J = 9 Hz, 1H), 7.44 (m, 3H), 7.20 (m, 4H), 7.05 (s, 1H), 6.85 (d, J = 9 Hz, 1H), 6.76 (d, J = 9 Hz, 1H), 6.64 (d, J = 9 Hz, 1H), 6.59 (s, 1H), 5.32 (bs, 1H, -OH), 4.28 (m, 4H), 2.63 (q, J = 8 Hz, 2H), 2.52 (d, J = 8 Hz, 2H), 2.38 (quintet, J = 8 Hz, 2H), 1.96 (heptet, J = 8 Hz, 1H), 1.23 (t, J = 9 Hz, 3H), 0.98 (d, J = 8 Hz, 6H); MS-FD m/e 559 (p + 1, 39), 558 (p, 100); IR (KBr, cm^{-1}) 3350 (b), 2958, 1699, 1604, 1457, 1222, 1112, 1062, 838, 756.

Analysis for $C_{34}H_{35}O_6F$:

Calc:	C,	73.10;	H,	6.31;
Found:	C,	73.32;	H,	6.50.

Example 11

2-[2-Butyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid hydrate



A. Preparation of 2-butyl-1,3-dimethoxybenzene.

1,3-Dimethoxybenzene (15.0 g, 109 mmol) was alkylated with 1-iodobutane as described above for the preparation of Example 10(A) except that the final reaction mixture was not refluxed. Purification via silica gel chromatography (ethyl acetate/hexane) provided 15.0 g (71%) of the title intermediate product as a yellow oil: NMR ($CDCl_3$) 7.18 (t, J = 8.2 Hz, 1H), 6.59 (d, J = 9.7 Hz, 2H), 3.84 (s, 6H), 2.70 (t, J = 8.7 Hz, 2H), 1.50 (hextet, J = 6 Hz, 2H), 1.44 (quintet, J = 6 Hz, 2H), 0.98 (t, J = 8.2 Hz, 3H); MS-FD m/e 194 (p).

B. Preparation of 2-(3-hydroxy-2-butylphenoxy)-benzoic acid methyl ester.

2-Butyl-1,3-dimethoxybenzene (14.98 g, 77.6 mmol) was de-methylated as described above for the preparation of Example 10(B) to provide 19 g crude product as a brown oil. A solution of 15 g of this material and potassium tert-butoxide (9.70 g, 86.5 mmol) in pyridine (150 mL) was added to a second solution of methyl 2-iodobenzoate (11.9 g, 180 mmol) and copper(I) iodide (17.3 g, 91.0 mmol) in pyridine (150 mL). The resulting mixture was refluxed for 36 hours. The mixture was cooled to room temperature, diluted with

water, and extracted three times with diethyl ether The combined ether fractions were filtered through a mat of Celite®, washed once with 5N aqueous hydrochloric acid, once with 2N aqueous sodium hydroxide, and filtered again through a mat of Celite®. The resulting solution was dried over magnesium sulfate, filtered, and evaporated *in vacuo*. Silica gel chromatography (ethyl acetate/hexane) provided 3.02 g (11%) of the title intermediate product as an orange oil: NMR ($CDCl_3$) 7.91 (d, J = 8 Hz, 1H), 7.41 (t, J = 8 Hz, 1H), 7.14 (t, J = 8 Hz, 1H), 6.97 (t, J = 9 Hz, 1H), 6.83 (d, J = 8 Hz, 1H), 6.59 (d, J = 8 Hz, 1H), 6.39 (d, J = 8 Hz, 1H), 5.04 (bs, 1H, -OH), 3.83 (s, 3H), 2.66 (t, J = 9 Hz, 2H), 1.54 (quintet, J = 5 Hz, 2H), 1.35 (hextet, J = 5 Hz, 2H), 0.91 (t, J = 8 Hz, 3H); MS-EI m/e 300 (p, 34), 225 (100), 213 (42), 197 (53), 107 (38); IR (mull, cm^{-1}) 3410, 2926, 1709, 1600, 1463, 1234, 1107, 1090, 992.

Analysis for $C_{18}H_{20}O_4$:

Calc:	C,	71.98;	H,	6.71;
Found:	C,	70.82;	H,	6.67.

C. Preparation of 2-[2-butyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-benzoic acid methyl ester.

2-(3-Hydroxy-2-butylphenoxy)benzoic acid methyl ester (700 mg, 1.76 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene as described above for the preparation of Example 5(A) to provide crude product as an oil. Purification via silica gel chromatography (ethyl acetate/hexane) provided 700 mg (60%) of the title intermediate product as a yellow oil: NMR ($CDCl_3$) 7.91 (d, J = 9 Hz, 1H), 7.58 (m, 2H), 7.38 (m, 6H), 7.18 (m, 5H), 6.88 (d, J = 10 Hz, 1H), 6.76 (d, J = 9 Hz, 1H), 6.68 (s, 1H), 6.47 (d, J = 9 Hz, 1H), 5.09 (s, 2H), 4.25 (m, 4H), 3.91 (s, 3H), 2.72 (m, 4H), 2.40 (quintet, J = 5 Hz, 2H), 1.60 (hextet, J = 5 Hz, 2H), 1.38

(m, 2H), 1.24 (t, J = 8 Hz, 3H), 0.99 (t, J = 8 Hz, 3H); IR ($CHCl_3$, cm^{-1}) 3024, 1717, 1602, 1465, 1453, 1306, 1234, 1086, 1014.

Analysis for $C_{42}H_{43}O_6F$:

Calc:	C,	76.11;	H,	6.54;
Found:	C,	75.82;	H,	6.50.

D. Preparation of 2-[2-butyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid hydrate.

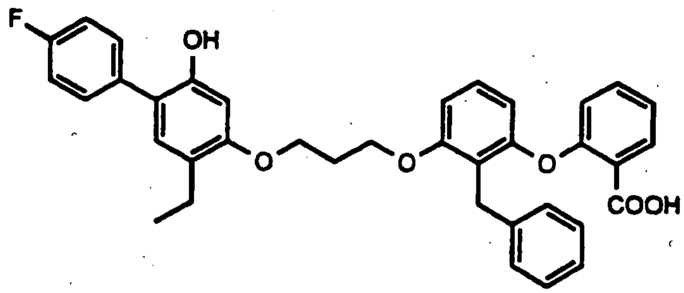
2-[2-Butyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (690 mg, 1.04 mmol) was submitted to de-benzylation conditions as described above for the preparation of Example 7(C). Hydrolysis of the resulting ester provided 114 mg (30%) of the title product as an off-white solid: mp 62-64°C; NMR (DMSO-d_6) 12.75 (bs, 1H, -COOH), 9.60 (bs, 1H, -OH), 7.69 (d, J = 7.3 Hz, 1H), 7.50 (m, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.00-7.18 (m, 4H), 6.96 (s, 1H), 6.69 (m, 2H), 6.56 (s, 1H), 6.31 (d, J = 8.2 Hz, 1H), 4.17 (t, J = 5.1 Hz, 2H), 4.09 (t, J = 5.4 Hz, 2H), 2.58 (t, J = 7.3 Hz, 2H), 2.48 (m, 2H), 2.21 (quintet, J = 5.0 Hz, 2H), 1.37 (hextet, J = 6.8 Hz, 2H), 1.21 (m, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.74 (t, J = 7.1 Hz, 3H); MS-FD m/e 559 (p + 1, 55), 558 (p, 100); IR (KBr, cm^{-1}) 3350 (b), 2963, 2933, 1738, 1605, 1497, 1461, 1455, 1236, 1118.

Analysis for $C_{34}H_{35}O_6F \cdot H_2O$:

Calc:	C,	70.81;	H,	6.47;
Found:	C,	71.19;	H,	6.52.

Example 12

2-[2-(Phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid



A. Preparation of 2-(phenylmethyl)-1,3-dimethoxybenzene.

1,3-Dimethoxybenzene (75.0 g, 391 mmol) was alkylated with benzyl bromide as described above for the preparation of Example 10(A) except that the final reaction mixture was not refluxed. Purification via silica gel chromatography (ether/hexane) provided 18.8 g (8%) of intermediate product as a white solid: 53-55°C; NMR ($CDCl_3$) 7.15-7.37 (m, 6H), 6.62 (d, J = 10 Hz, 2H), 4.12 (s, 2H), 3.87 (s, 6H); MS-FD m/e 229 (p + 1, 17), 228 (p, 100); IR (KBr, cm^{-1}) 2925, 2839, 1594, 1476, 1435, 1259, 1197, 1106, 700.

Analysis for $C_{15}H_{16}O_2$:

Calc:	C,	78.92;	H,	7.06;
Found:	C,	79.21;	H,	7.33.

B. Preparation of 2-(phenylmethyl)-1,3-dihydroxybenzene.

2-(Phenylmethyl)-1,3-dimethoxybenzene (15.0 g, 65.8 mmol) was de-methylated as described above for the preparation of Example 10(B). Purification via silica gel chromatography (ethyl acetate/hexane) provided 7.76 g (60%) of title intermediate product as an off-white crystalline

material: mp 81-83°C; NMR ($CDCl_3$) 7.18-7.23 (m, 5H), 7.01 (t, J = 9 Hz, 1H), 6.43 (d, J = 10 Hz, 2H), 5.38 (bs, 2H, -OH), 4.18 (s, 2H); MS-FD m/e 201 (p + 1, 23), 200 (p, 100); IR (KBr, cm^{-1}) 3505 (b), 1618, 1464, 1360, 1292, 1183, 1012, 739.

Analysis for $C_{13}H_{12}O_2$:

Calc:	C,	77.98;	H,	6.04;
Found:	C,	77.69;	H,	5.99.

C. Preparation of 2-[3-hydroxy-2-(phenylmethyl)-phenoxy]benzoic acid methyl ester.

2-(Phenylmethyl)-1,3-dihydroxybenzene (14.5 g, 87.3 mmol) was submitted to Ullmann coupling conditions with methyl 2-iodobenzoate as described above for the preparation of Example 2(A). Purification of the crude product via silica gel chromatography (ethyl acetate/hexane) provided 900 mg (7%) of title intermediate product as a white crystalline material: mp 79-81°C; NMR ($CDCl_3$) 7.93 (d, J = 9 Hz, 1H), 7.35 (m, 3H), 7.27 (m, 2H), 7.13 (m, 2H), 7.04 (d, J = 9 Hz, 1H), 6.83 (d, J = 9 Hz, 1H), 6.63 (d, J = 9 Hz, 1H), 6.41 (d, J = 9 Hz, 1H), 5.43 (bs, 1H, -OH), 4.14 (s, 2H), 3.79 (s, 3H); MS-FD m/e 335 (p + 1, 23), 334 (p, 100); IR (KBr, cm^{-1}) 3327 (b), 1687, 1598, 1453, 1315, 1233, 1008, 754.

Analysis for $C_{21}H_{18}O_4$:

Calc:	C,	75.43;	H,	5.43;
Found:	C,	75.21;	H,	5.57.

D. Preparation of 2-[2-(phenylmethyl)-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]-phenoxy]benzoic acid methyl ester.

2-[3-Hydroxy-2-(phenylmethyl)phenoxy]benzoic acid methyl ester (840 mg, 2.51 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene as described above for the preparation of

Example 5(A). Purification via silica gel chromatography (ethyl acetate/hexane) provided 680 mg (40%) of desired title intermediate product as a glass: NMR ($CDCl_3$) 8.01 (d, J = 8 Hz, 1H), 7.65 (m, 2H), 7.40 (m, 8H), 7.15-7.30 (m, 8H), 6.88 (d, J = 10 Hz, 1H), 6.80 (d, J = 10 Hz, 1H), 6.63 (s, 1H), 6.48 (d, J = 9 Hz, 1H), 5.09 (s, 2H), 4.34 (t, 7 Hz, 2H), 4.22 (s, 2H), 4.20 (t, J = 7 Hz, 2H), 3.84 (s, 3H), 2.77 (q, J = 8 Hz, 2H), 2.40 (quintet, J = 8 Hz, 2H), 1.38 (t, J = 9 Hz, 3H); MS-FD m/e 698 (p + 1, 48), 697 (p, 100); IR ($CHCl_3$, cm^{-1}) 3015, 2975, 1717, 1604, 1496, 1453, 1306, 1081.

Analysis for $C_{45}H_{41}O_6F$:

Calc:	C,	77.57;	H,	5.93;
Found:	C,	77.80;	H,	6.08.

E. Preparation of 2-[2-(phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid.

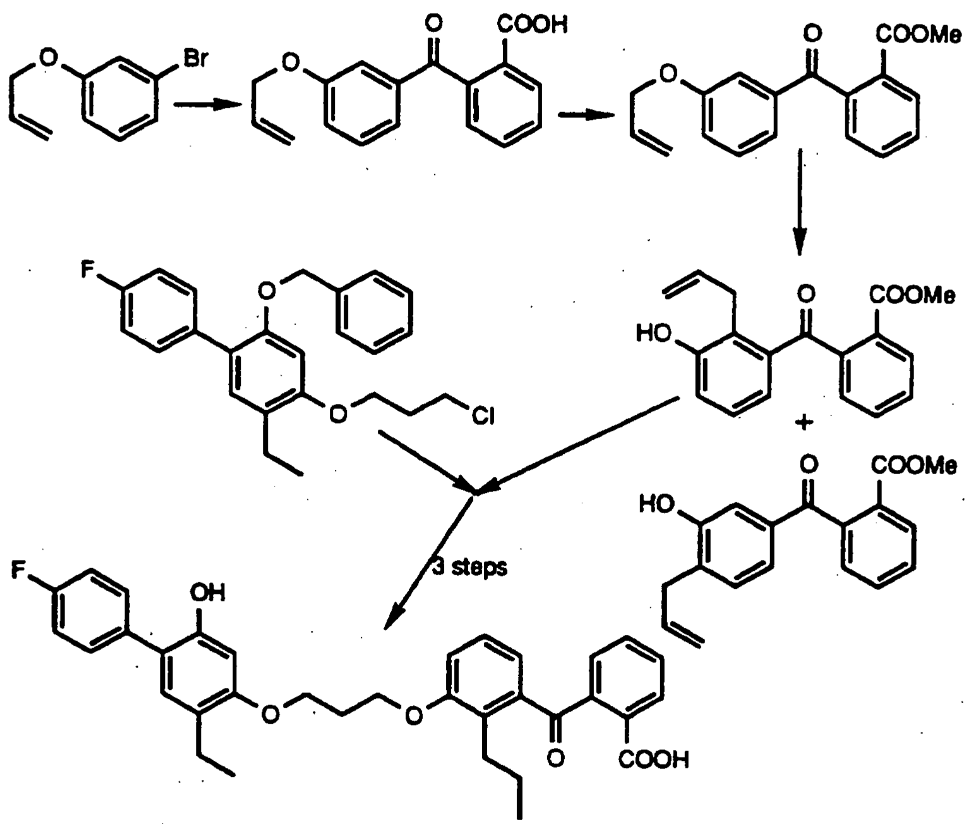
2-[2-(Phenylmethyl)-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (660 mg, 0.947 mmol) was submitted to de-benzylation conditions and hydrolysis. Purification via silica gel chromatography (ethyl acetate/hexane) provided 450 mg (80%) the desired title product as a glass: NMR ($CDCl_3$) 8.16 (dd, J = 7.8, 1.8 Hz, 1H), 7.43 (m, 2H), 7.35 (m, 1H), 7.05-7.32 (m, 9H), 7.02 (s, 1H), 6.86 (d, 8.4 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.46 (s, 1H), 4.28 (t, J = 4.6 Hz, 2H), 4.10 (t, J = 4.1 Hz, 2H), 4.08 (s, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.33 (quintet, J = 5.1 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H); MS-FD m/e 593 (p, 100), 592 (p - 1, 89); IR ($CHCl_3$, cm^{-1}) 3375 (b), 3020, 2970, 1738, 1605, 1496, 1455, 1068.

Analysis for $C_{37}H_{33}O_6F$:

Calc:	C,	74.98;	H,	5.61;
Found:	C,	75.21;	H,	5.72.

Example 13

2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid



A. Preparation of 2-[3-(allyloxy)benzoyl]benzoic acid.

To a solution of 3-(allyloxy)bromobenzene (15.0 g, 70.5 mmol) in tetrahydrofuran (750 mL) at -70°C was added 1.6M n-butyllithium (44.1 mL, 70.5 mmol). After stirring for 1 hour, a solution of phthalic anhydride (11.4 g, 77.0 mmol) in tetrahydrofuran (100 mL, previously cooled to -70°C) was added over 1 hour. The mixture was allowed to warm to room temperature and stirred for 3 hours. The mixture was diluted with saturated ammonium chloride solution and extracted with diethyl ether. The organic

layer was washed three times with 1N sodium hydroxide solution and the combined aqueous layers were back-extracted with a fresh portion of diethyl ether. The aqueous layer was adjusted to pH~3 with aqueous hydrochloric acid and extracted three times with fresh diethyl ether. The combined organic layers were washed once with water, once with saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to reveal an off-white solid. Recrystallization from ether/hexane provided 10.3 g (52%) of the title intermediate as a white crystalline material: mp 109°C; NMR ($CDCl_3$) 8.20 (d, J = 8 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.60 (t, J = 8 Hz, 1H), 7.30-7.45 (m, 3H), 7.28 (d, J = 8 Hz, 1H), 7.20 (d, J = 8 Hz, 1H), 6.02 (m, 1H), 5.35 (d, J = 16 Hz, 1H), 5.30 (d, J = 11 Hz, 1H), 4.55 (d, J = 6 Hz, 2H); MS-FD m/e 283 (p + 1, 27), 282 (p, 100).

Analysis for $C_{17}H_{14}O_4$:

Calc:	C,	72.33;	H,	5.00;
Found:	C,	72.07;	H,	5.22.

B. Preparation of 2-[3-(allyloxy)benzoyl]benzoic acid methyl ester.

A solution of 2-[3-(allyloxy)benzoyl]benzoic acid (9.00 g, 31.9 mmol) in methanol (100 mL) was saturated with hydrogen chloride gas. The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and diluted with diethyl ether. The resulting solution was washed sequentially with a saturated sodium bicarbonate solution, water, and a saturated sodium chloride solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The resulting pale yellow oil solidified upon standing to provide 9.45 g (100%) of the desired title product as a white solid: mp 50-52°C; NMR ($CDCl_3$) 8.05 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.40 (m, 2H), 7.32 (t, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H),

7.14 (d, J = 8 Hz, 1H), 6.08 (m, 1H), 5.40 (d, J = 16 Hz, 1H), 5.30 (d, J = 11 Hz, 1H), 4.78 (d, J = 4 Hz, 2H), 3.62 (s, 3H); MS-FD m/e 297 (p + 1, 40), 296 (p, 100); IR.

Analysis for $C_{18}H_{16}O_4$:

Calc:	C,	72.46;	H,	5.44;
Found:	C,	72.75;	H,	5.58.

C. Preparation of 2-[3-hydroxy-2-[3-(1-propenyl)]-benzoyl]benzoic acid methyl ester and 2-[3-hydroxy-4-[3-(1-propenyl)]benzoyl]benzoic acid methyl ester.

2-[3-(Allyloxy)benzoyl]benzoic acid methyl ester (6.70 g, 20.2 mmol) was heated neat at 175°C for 30 hours. The product mixture was cooled to room temperature and purified via silica gel chromatography (95:5 methylene chloride/ethyl acetate) to provide 3.62 g (54%) of 2-[3-hydroxy-2-[3-(1-propenyl)]-benzoyl]benzoic acid methyl ester and 1.44 g (21%) of 2-[3-hydroxy-4-[3-(1-propenyl)]benzoyl]benzoic acid methyl ester as white solids.

2-[3-Hydroxy-2-[3-(1-propenyl)]benzoyl]benzoic acid methyl ester, mp 107-109°C; NMR ($CDCl_3$) 7.91 (dd, J = 7.8, 2.2 Hz, 1H), 7.43-7.63 (m, 3H), 7.08 (m, 1H), 7.02 (d, J = 8 Hz, 1H), 6.80 (dd, J = 8, 2 Hz, 1H), 6.15 (m, 1H), 5.42 (bs, 1H, -OH), 5.23 (d, J = 16 Hz, 1H), 5.16 (d, J = 11 Hz, 1H), 3.81 (d, J = 6 Hz, 2H), 3.68 (s, 3H); MS-FD m/e 297 (p + 1, 40), 296 (p, 100), 278 (45); IR.

Analysis for $C_{18}H_{16}O_4$:

Calc:	C,	72.96;	H,	5.44;
Found:	C,	73.26;	H,	5.54.

2-[3-Hydroxy-4-[3-(1-propenyl)]benzoyl]benzoic acid methyl ester, mp 139-140°C; NMR ($CDCl_3$) 8.08 (dd, J = 7.9, 3.1 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.35 (s, 1H), 7.16 (s, 2H), 6.00 (m,

1H), 5.62 (bs, 1H, -OH), 5.15 (m, 2H), 3.65 (s, 3H), 3.47 (d, J = 5 Hz, 2H); MS-FD m/e 297 (p + 1, 20), 296 (p, 100); IR.

Analysis for $C_{18}H_{16}O_4$:

Calc:	C,	72.96;	H,	5.44;
Found:	C,	73.11;	H,	5.50.

D. Preparation of 2-[2-[3-(1-propenyl)]-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]-benzoyl]benzoic acid methyl ester.

2-[3-Hydroxy-2-[3-(1-propenyl)]benzoyl]benzoic acid methyl ester (520 mg, 1.75 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene as described above for the preparation of Example 5(A). Recrystallization of the crude product from ether/hexane provided 750 mg (65%) of the desired title intermediate as a white solid: mp 90-91°C; NMR ($CDCl_3$) 7.91 (m, 1H), 7.53 (m, 4H), 7.45 (m, 1H), 7.32 (m, 5H), 7.02-7.22 (m, 5H), 6.85 (d, J = 8 Hz, 1H), 6.61 (s, 1H), 6.10 (m, 1H), 5.04 (d, J = 16 Hz, 1H), 5.03 (s, 2H), 4.99 (d, J = 11 Hz, 1H), 4.23 (m, 4H), 3.77 (d, J = 7 Hz, 2H), 3.66 (s, 3H), 1.64 (q, J = 6 Hz, 2H), 2.37 (quintet, J = 6 Hz, 2H), 1.19 (t, J = 8 Hz, 3H); MS-FD m/e 659 (p + 1, 44), 658 (p, 100).

Analysis for $C_{42}H_{39}O_6F$:

Calc:	C,	76.58;	H,	5.97;
Found:	C,	76.79;	H,	6.09.

E. Preparation of 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid.

2-[2-[3-(1-Propenyl)]-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]benzoyl]benzoic acid methyl ester (318 mg, 0.483 mmol) was submitted to hydrogenation conditions as described above for the

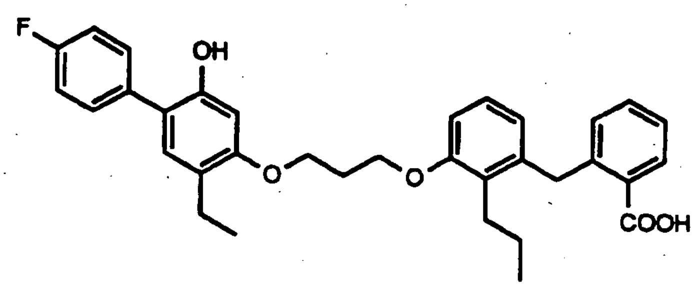
preparation of Example 7(C). Hydrolysis of the resulting ester and purification via silica gel chromatography (ethyl acetate/hexane) provided 150 mg (56%) of the title product as a glass: NMR (DMSO-d_6) 10.15 (bs, 1H, -OH), 7.84 (m, 1H), 7.49 (m, 2H), 7.41 (m, 2H), 6.98-7.23 (m, 5H), 6.96 (s, 1H), 6.62 (d, J = 7.2 Hz, 1H), 6.59 (s, 1H), 4.18 (t, J = 5.3 Hz, 2H), 4.06 (t, J = 5.8 Hz, 2H), 2.85 (m, 2H), 2.49 (m, 2H), 2.20 (quintet, J = 5.2 Hz, 2H), 1.57 (hextet, J = 5 Hz, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); IR, MS.

Analysis for $C_{34}H_{33}O_6F$:

Calc:	C,	73.36;	H,	5.98;
Found:	C,	69.71:	H,	5.90.

Example 14

2-[[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl]benzoic acid



A. Preparation of 2-[(3-hydroxy-2-propylphenyl)-methyl]benzoic acid methyl ester.

A mixture of 2-[3-hydroxy-2-[3-(1-propenyl)]benzoyl]-benzoic acid methyl ester (3.00 g, 10.1 mmol), concentrated sulfuric acid (1 mL), and 5% palladium on carbon (1.5 g) in methanol (95 mL) was hydrogenated at 4 atmospheres for 18 hours. The mixture was concentrated *in vacuo* to a volume of approximately 30 mL, filtered, and saturated with hydrogen chloride gas. The resulting mixture was stirred

for 18 hours, then concentrated *in vacuo*. The residue was dissolved in diethyl ether and washed with a saturated sodium bicarbonate solution. The aqueous layer was back-extracted with a fresh portion of diethyl ether. The combined organic layers were washed with a saturated sodium chloride solution, dried, filtered, and concentrated *in vacuo* to provide 2.60 g (90%) of the title intermediate as an orange oil: NMR ($CDCl_3$) 7.97 (d, J = 7 Hz, 1H), 7.38 (t, J = 7 Hz, 1H), 7.28 (t, J = 7 Hz, 1H), 7.02 (m, 2H), 6.70 (d, J = 7 Hz, 1H), 6.54 (d, J = 7 Hz, 1H), 5.20 (bs, 1H, -OH), 4.45 (s, 2H), 3.89 (s, 3H), 2.58 (t, J = 7 Hz, 2H), 1.52 (hextet, J = 7 Hz, 2H), 0.92 (t, J = 7 Hz, 3H); MS-FD m/e 285 (p + 1, 23), 284 (100); IR.

B. Preparation of 2-[[2-propyl-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]-methyl]benzoic acid methyl ester.

2-[(3-Hydroxy-2-propylphenyl)methyl]benzoic acid methyl ester (2.00 g, 4.68 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene as described above for the preparation of Example 5(A). Recrystallization of the crude product from hexane provided 1.72 g (38%) of the title intermediate as a white solid: mp 83-84°C; NMR ($CDCl_3$) 7.94 (d, J = 8 Hz, 1H), 7.53 (m, 2H), 7.25-7.40 (m, 7H), 7.05-7.15 (m, 4H), 7.00 (d, J = 7 Hz, 1H), 7.81 (d, J = 7 Hz, 1H), 6.62 (s, 1H), 6.58 (d, J = 7 Hz, 1H), 5.02 (s, 2H), 4.42 (s, 2H), 4.21 (m, 4H), 3.88 (s, 3H), 2.54-2.68 (m, 4H), 2.32 (quintet, J = 6 Hz, 2H), 1.50 (hextet, J = 6 Hz, 2H), 1.21 (t, J = 8 Hz, 3H), 0.96 (t, J = 8 Hz, 3H); MS-FD m/e 648 (p + 1, 40), 647 (p, 100); IR ($CHCl_3$, cm^{-1}) 2964, 1718, 1603, 1497, 1459, 1143.

Analysis for $C_{42}H_{43}O_5F$:

Calc:	C,	77.99;	H,	6.70;
Found:	C,	79.47;	H,	6.76.

C. Preparation of 2-[[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl]-benzoic acid.

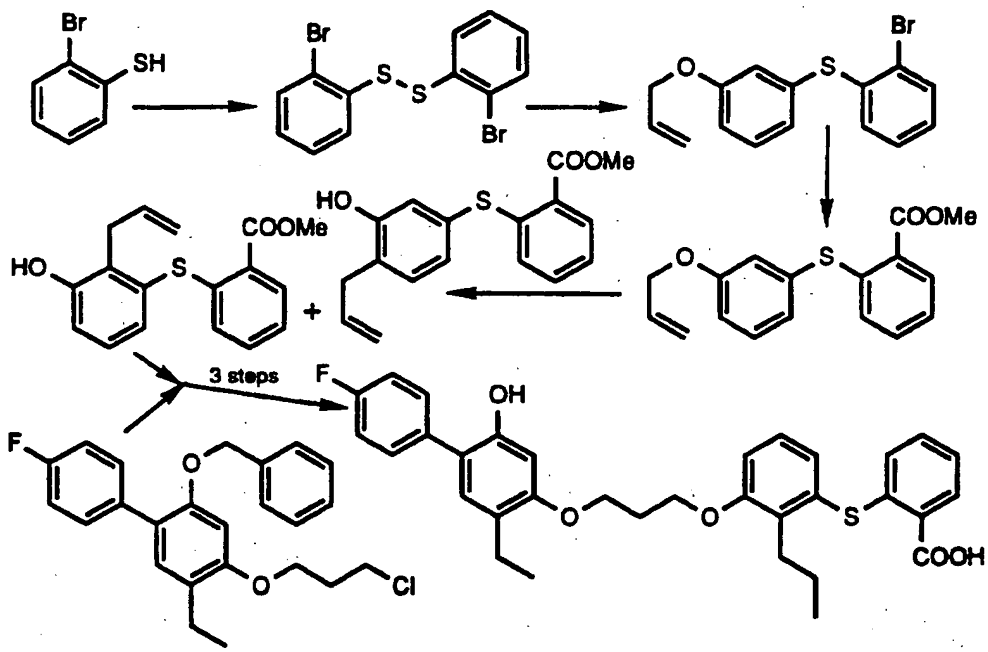
2-[[2-Propyl-3-[3-[2-ethyl-5-(phenylmethoxy)-4-(4-fluorophenyl)phenoxy]propoxy]phenyl]methyl]benzoic acid methyl ester (1.50 mg, 2.32 mmol) was submitted to de-benzylation conditions as described above for the preparation of Example 7(C). Hydrolysis of the resulting ester followed by recrystallization of the crude product from ether/hexane provided 860 mg (68%) of the desired title product as a white solid: mp 150-151°C; NMR ($CDCl_3$) 8.11 (dd, J = 7.3, 0.8 Hz, 1H), 7.45 (m, 2H), 7.30 (t, J = 7 Hz, 1H), 6.95-7.25 (m, 5H), 6.81 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 7.4 Hz, 1H), 6.52 (s, 1H), 4.50 (s, 2H), 4.21 (m, 4H), 2.62 (m, 4H), 2.35 (quintet, J = 6.0 Hz, 2H), 1.46 (hextet, J = 7.6 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); MS-FD m/e 543 (p + 1, 40), 542 (p, 100); IR ($CHCl_3$, cm^{-1}) 3400 (b), 2966, 1696, 1603, 1496, 1459, 1238, 1146, 1111.

Analysis for $C_{34}H_{35}O_5F$:

Calc:	C,	75.26;	H,	6.50;
Found:	C,	75.26;	H,	6.62.

Example 15

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid



A. Preparation of 2-bromophenyldisulfide.

To a mixture of 2-bromothiophenol (20.0 g, 106 mmol) and 2N sodium hydroxide solution (100 mL) in diethyl ether (400 mL) was added solid iodine (13.4 g, 53.0 mmol) in portions. The mixture was stirred at room temperature for 1 hour at which time the ether layer was separated. The aqueous layer was extracted with a fresh portion of ether and the combined ether layers were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide 17.2 g (43%) of intermediate product as a white solid: mp 95-97°C; NMR ($CDCl_3$) 7.52 (m, 4H), 7.25 (t, J = 9.7 Hz, 2H), 7.06 (t, J = 9.7 Hz, 2H); MS-FD m/e 380 (p +

4, 20), 379 (p + 3, 30), 378 (p + 2, 85), 376 (p, 100), 374 (p - 2, 75); IR.

Analysis for $C_{12}H_8Br_2S_2$:

Calc:	C,	38.32;	H,	2.14;
Found:	C,	38.61;	H,	2.13.

B. Preparation of 2-[3-(allyloxy)thiophenoxy]-bromobenzene.

To a solution of 3-(allyloxy)bromobenzene (8.20 g, 38.7 mmol) in tetrahydrofuran (600 mL) at -74°C was added 1.6M n-butyllithium (24.2 mL, 38.7 mmol). After stirring for 30 minutes this solution was cannulated into a solution of 2-bromophenyl-disulfide (16.0 g, 42.5 mmol) in tetrahydrofuran (160 mL) at -74°C. The resulting mixture was allowed to warm to room temperature then diluted with saturated ammonium chloride solution and filtered. The aqueous layer was extracted with three times with diethyl ether and the combined organic layers were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Purification via silica gel chromatography provided 9.40 g (76%) of the title intermediate as a light yellow oil: NMR ($CDCl_3$) 7.58 (d, J = 7 Hz, 1H), 7.27 (t, J = 7 Hz, 1H), 7.17 (t, J = 7 Hz, 1H), 6.85-7.15 (m, 5H), 6.04 (m, 1H), 5.41 (d, J = 14 Hz, 1H), 5.30 (d, J = 10 Hz, 1H), 4.52 (d, J = 4 Hz, 2H); MS-FD m/e 322 (p, 100), 320 (p, 75); IR (KBr, cm^{-1}) 3223 (b), 1688, 1345, 1161, 1013, 678.

Analysis for $C_{15}H_{13}OBrS$:

Calc:	C,	56.09;	H,	4.08;
Found:	C,	56.31;	H,	4.22.

C. Preparation of 2-[3-(allyloxy)thiophenoxy]-benzoic acid methyl ester.

To a solution of 2-[3-(allyloxy)thiophenoxy]-bromobenzene (9.00 g, 28.0 mmol) in tetrahydrofuran (175 mL) at -78°C was added 1.6M n-butyllithium (19.2 mL, 30.8 mmol) dropwise. After stirring for 15 minutes, the solution was saturated with carbon dioxide gas resulting in a thick gel. Tetrahydrofuran (50 mL) was added and the resulting mixture allowed to warm to room temperature. The mixture was diluted with saturated ammonium chloride solution. The aqueous layer was extracted once with diethyl ether and the combined organic layers were concentrated *in vacuo*. The residue was dissolved in a fresh portion of ether and extracted with 1N aqueous sodium hydroxide. The aqueous layer was washed with a fresh portion of ether and acidified with aqueous hydrochloric acid. The resulting aqueous layer was extracted with a fresh portion of ether. The organic layer was washed with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude acid was dissolved in methanol (125 mL) and the resulting solution saturated with hydrogen chloride gas. After stirring for 18 hours, the reaction mixture was concentrated *in vacuo*, the residue dissolved in ether, and the resulting solution washed with saturated sodium bicarbonate solution. The aqueous layer was back-extracted with a fresh portion of ether and the combined organic layers were washed once with water, once with a saturated sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (ethyl acetate/hexane) provided 4.80 g (68%) of the desired title intermediate as a faint yellow oil: NMR ($CDCl_3$) 7.99 (dd, J = 7.8, 1.4 Hz, 1H), 7.33 (t, J = 7 Hz, 1H), 7.25 (t, J = 7 Hz, 1H), 7.15 (m, 3H), 7.00 (dd, J = 8.7, 2.8 Hz, 1H), 6.88 (d, J = 8 Hz, 1H), 6.04 (m, 1H), 5.42 (d, J = 14 Hz, 1H), 5.30 (d, J = 11

Hz, 1H), 4.53 (d, J = 3.9 Hz, 2H), 3.97 (s, 3H); MS-FD m/e 301 (p + 1, 25), 300 (p, 100); IR ($CHCl_3$, (cm^{-1}) 3025, 1712, 1590, 1463, 1437, 1254, 1060.

Analysis for $C_{17}H_{16}O_3S$:

Calc:	C,	67.98;	H,	5.37;
Found:	C,	67.86;	H,	5.29.

D. Preparation of 2-[3-hydroxy-2-[3-(1-propenyl)]-thiophenoxy]benzoic acid methyl ester and 2-[3-hydroxy-4-[3-(1-propenyl)]thiophenoxy]benzoic acid methyl ester.

2-[3-(Allyloxy)thiophenoxy]benzoic acid methyl ester (5.40 g, 15.0 mmol) was heated neat at 175°C for 29 hours. The product mixture was cooled to room temperature and purified via silica gel chromatography (methylene chloride) to provide 2.22 g (41%) of 2-[3-hydroxy-2-[3-(1-propenyl)]thio-phenoxy]benzoic acid methyl ester and 1.46 g (27%) of 2-[3-hydroxy-4-[3-(1-propenyl)]thiophenoxy]benzoic acid methyl ester as white solids.

2-[3-Hydroxy-2-[3-(1-propenyl)]thiophenoxy]benzoic acid methyl ester, mp 72-74°C; NMR (DMSO-d_6) 9.79 (s, 1H, -OH), 7.89 (d, J = 8 Hz, 1H), 7.33 (t, J = 7 Hz, 1H), 7.09-7.23 (m, 2H), 6.94 (m, 2H), 6.62 (dd, J = 7, 1 Hz, 1H), 5.78 (m, 1H), 4.70-4.83 (m, 2H), 3.86 (s, 3H), 3.37 (d, J = 5 Hz, 2H); MS-FD m/e 301 (p + 1, 21), 300 (p, 100); IR ($CHCl_3$, cm^{-1}) 3595, 3350 (b), 3029, 3010, 2954, 1711, 1420, 1436, 1273, 1146, 1060.

Analysis for $C_{17}H_{16}O_3S$:

Calc:	C,	67.98;	H,	5.37;
Found:	C,	68.28;	H,	5.41.

2-[3-Hydroxy-4-[3-(1-propenyl)]thiophenoxy]benzoic acid methyl ester, mp 96-97°C; NMR (DMSO-d_6) 9.78 (s, 1H, -OH), 7.89 (d, J = 8 Hz, 1H), 7.40 (t, J = 7 Hz, 1H), 7.12-7.25 (m, 2H), 6.93 (s, 1H), 6.91 (d, J = 8 Hz, 1H), 6.81 (d, J = 8 Hz, 1H), 5.87 (m, 1H), 5.00-5.12 (m, 2H), 3.85 (s, 3H), 3.30 (d, J = 4 Hz, 2H); MS-FD m/e 301 (p + 1, 45),

300 (p, 100); IR ($CHCl_3$, cm^{-1}) 3595, 3300(b), 3029, 3010, 2954, 1711, 1436, 1310, 1255, 942.

Analysis for $C_{17}H_{16}O_3S$:

Calc:	C,	67.98;	H,	5.37;
Found:	C,	68.04;	H,	5.47.

E. Preparation of 2-[2-[3-(1-propenyl)]-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]-thiophenoxy]benzoic acid methyl ester.

2-[3-Hydroxy-2-[3-(1-propenyl)]thiophenoxy]benzoic acid methyl ester (2.00 g, 6.66 mmol) was alkylated with 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene as described above for the preparation of Example 5(A). Purification via silica gel chromatography (hexane/diethyl ether) provided 2.90 g (66%) of desired intermediate product as a white solid: mp 76-77°C; NMR ($CDCl_3$) 8.03 (dd, J = 7.6, 1.2 Hz, 1H), 7.54 (m, 2H), 7.17-7.40 (m, 8H), 6.98-7.18 (m, 5H), 6.71 (d, J = 7.9 Hz, 1H), 6.62 (s, 1H), 5.87 (m, 1H), 5.03 (s, 2H), 4.83-4.95 (m, 2H), 4.26 (t, J = 7 Hz, 2H), 4.21 (t, J = 7 Hz, 2H), 3.98 (s, 3H), 3.62 (d, J = 6.3 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 2.33 (quintet, J = 5.8 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H); MS-FD m/e 664 (p + 2, 40), 663 (p + 1, 70), 662 (p, 100); IR ($CHCl_3$, cm^{-1}) 3011, 2970, 2940, 2890, 1712, 1497, 1452, 1298, 1255, 1145, 1060.

Analysis for $C_{41}H_{39}O_5FS$:

Calc:	C,	74.30;	H,	5.93;
Found:	C,	74.46;	H,	6.13.

F. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid methyl ester.

2-[2-[3-(1-Propenyl)]-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]-thiophenoxy]benzoic acid methyl ester (2.70 g, 4.07 mmol) was hydrogenated as described above for the preparation of Example 7(C) to provide an oil (~2 g). A solution of this material (1.39 g) in methylene chloride (25 mL) at -78°C was treated with 1M boron tribromide (3.61 mL, 3.61 mmol) and allowed to stir for 1 hour. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo* to provide a yellow oil. Purification via silica gel chromatography provided 770 mg (47%) of the title intermediate as a white solid: mp 105-106°C; NMR ($CDCl_3$) 8.02 (dd, J = 7.6, 1.2 Hz, 1H), 7.43 (m, 2H), 7.07-7.30 (m, 8H), 6.98 (m, 2H), 6.71 (d, J = 7.9 Hz, 1H), 6.57 (s, 1H), 5.10 (bs, 1H, -OH), 4.24 (m, 2H), 3.98 (s, 3H), 2.83 (t, J = 7 Hz, 2H), 2.65 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 5 Hz, 2H), 1.52 (hextet, J = 6 Hz, 2H), 1.21 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); MS-FD m/e 575 (p + 1, 20), 574 (p, 100); IR.

G. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid methyl ester (700 mg, 1.22 mmol) was hydrolyzed to provide 689 mg (100%) of the desired title product as a white solid: mp 153-155°C; NMR ($CDCl_3$) 8.13 (dd, J = 8.2, 0.9 Hz, 1H), 7.42 (m, 2H), 7.10-7.33 (6H), 6.99 (m, 2H), 6.72 (d, J = 7.9 Hz, 1H), 6.55 (s, 1H), 4.90 (bs, 1H, -OH), 4.24 (m, 4H), 2.82 (t, J = 6 Hz, 2H), 2.63 (q, J = 7.5 Hz, 2H), 2.34 (quintet, J = 6 Hz, 2H), 1.51 (hextet, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); MS-FD m/ 561 (p +

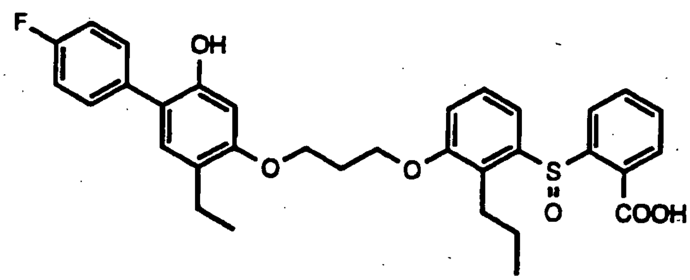
1, 20), 560 (p, 100); IR ($CHCl_3$, cm^{-1}) 2967, 1700, 1603, 1497, 1451, 1147, 1043.

Analysis for $C_{33}H_{33}O_5FS$:

Calc:	C,	70.69;	H,	5.93;
Found:	C,	70.43;	H,	5.97.

Example 16

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfinyl]benzoic acid



To a solution of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid (450 mg, 0.803 mmol) in methylene chloride (10 mL) at -78°C was added a solution of 85% m-chloroperoxybenzoic acid (138 mg) in methylene chloride (2 mL). After 40 minutes the mixture was concentrated *in vacuo*. Purification of the residue via silica gel chromatography (95% chloroform/4.5% methanol/0.5% acetic acid) provided 380 mg (80%) of the title product as an off-white solid: mp >100°C (dec); NMR ($CDCl_3$) 8.53 (d, J = 8 Hz, 1H), 8.14 (d, J = 8 Hz, 1H), 7.93 (t, J = 8 Hz, 1H), 7.63 (t, J = 8 Hz, 1H), 7.43 (m, 2H), 7.13 (m, 2H), 6.94-7.06 (m, 2H), 6.88 (d, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 7.46 (s, 1H), 6.38 (bs, 1H, -OH), 4.15 (m, 4H), 3.32 (m, 1H), 3.08 (m, 1H), 2.57 (q, J = 7.5 Hz, 2H), 2.29 (quintet, J = 6 Hz, 2H), 1.75 (m, 2H), 1.17 (t, J = 7.5 Hz, 3H), 1.05 (t, J =

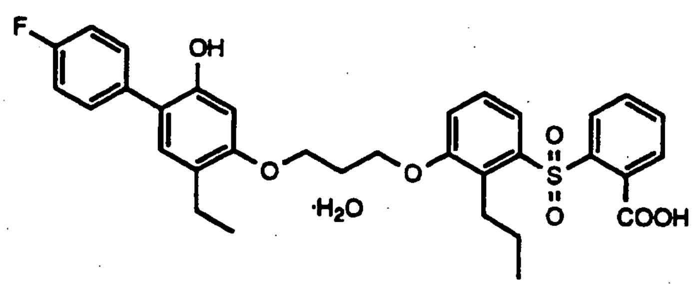
7.3 Hz, 3H); MS (high resolution) calc 577.202642 (MH^+), found 577.203800; IR ($CHCl_3$, cm^{-1}) 2969, 1708, 1497, 1455, 1266, 1146, 1018.

Analysis for $C_{33}H_{33}O_6FS$:

Calc:	C,	68.73;	H,	5.77;
Found:	C,	67.54;	H,	5.69.

Example 17

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfonyl]benzoic acid hydrate



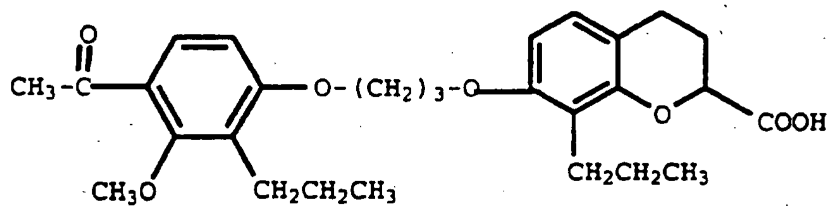
To a solution of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenylsulfinyl]-benzoic acid (150 mg, 0.260 mmol) in methylene chloride (3.0 mL) at 0°C was added a solution of 85% m-chloroperoxybenzoic acid (53 mg) in methylene chloride (1 mL). After 1 hour the mixture was warmed to 4°C and stirred for 18 hours. The mixture was concentrated *in vacuo;* purification of the residue via silica gel chromatography (90% chloroform/9.5% methanol/0.5% acetic acid) provided 90 mg (58%) of the title product as a white solid: mp 80-90°C; NMR (DMSO-d_6) 7.88 (m, 2H), 7.55-7.78 (m, 3H), 7.50 (m, 2H), 7.33 (m, 2H), 7.04 (m, 2H), 6.95 (s, 1H), 6.51 (s, 1H), 4.19 (t, J = 4.8 Hz, 2H), 4.05 (t, J = 5.8 Hz, 2H), 2.69 (m, 2H), 2.44 (q, J = 5.8 Hz, 2H), 2.19 (m, 2H), 0.90-1.10 (m, 5H), 0.71 (t, J = 4.5 Hz, 3H); MS-FD m/e 595 (p + 2, 30), 594 (p + 1, 40), 593 (p, 100); IR ($CHCl_3$, cm^{-1}) 2966, 1730, 1603, 1497, 1299, 1146.

Analysis for $C_{33}H_{33}O_7FS \cdot H_2O$:

Calc:	C,	64.90;	H,	5.78;
Found:	C,	64.89;	H,	5.67.

Example 18

8-Propyl-7-[3-[4-acetyl-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid



The title compound was prepared in a manner analogous to that of Example 1 of U.S. Patent No. 4,889,871.

Assay for Reversal of Adriamycin Resistance

HL60/ADR is a continuous cell line, which was selected for Adriamycin™ resistance by culturing HL60, a human acute myeloblastic leukemia cell line, in increasing concentrations of Adriamycin™ until a highly resistant variant was attained. (McGrath, T., et al., Biochem. Pharmacol., **38**: 3611, (1989); Marquardt, D. and Center, M. S., Cancer Res., **52**: 3157, (1992); and Marquardt, D., et al., Cancer Res., **50**: 1426, (1990))

HL60/ADR cells were grown in RPMI 1640 (Gibco) containing 10% fetal bovine serum (FBS) and 250 µg/ml gentamicin™ (Sigma). Cells were harvested; washed twice with assay medium (same as culture media); counted; and diluted to 2 x 10^5 cells/ml in assay medium. Fifty µl of cells were aliquoted into wells of a 96 well tissue culture plate. One column of each 96 well plate served as a negative control and received assay medium containing no cells.

Test compounds and references compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 5 mM. Samples were diluted to 20 μM in assay medium and 25 μl of each test compound was added to 6 wells. Assay standards were run in quadruplicate. 25 μl of 0.4% DMSO was added to four wells as a solvent control. Assay media was added to all wells to achieve a final volume of 100 μl per well.

The plates were incubated at 37° Centigrade for 72 hours in a humidified incubator with a 5% CO_2 atmosphere. A CellTiter96 Aqueous Assay Kit (Promega) was used to measure cell viability and vitality via oxidation of a tetrazolium salt. The assay was performed in accordance with the vendors instructions, which required 2 ml of MTS reagent being mixed with 0.1 ml of PMS reagent and 20 μl of this solution was added to each well. The plates were incubated for 3 hours at 37° C. Absorbance was determined at 490 nm using a microtitre plate reader.

The ability of a test compound to reverse the resistance of HL60/ADR cells to Adriamycin was determined by comparison of the absorbance of the wells containing a test compound in addition to Adriamycin with the absorbance of wells containing Adriamycin without a test compound. Controls were used to eliminate background and to ensure the results were not artifactual. The results of the assay are expressed as percent inhibition of cell growth. Adriamycin alone at the tested concentration does not usually inhibit the growth of HL60/ADR cells.

Table 1

Example	% Inhibition
1	54%
2	63%
3	55%
4	38%
5	23%
6	35%
7	72%
8	57%
9	61%
10	49%
11	47%
12	62%
13	64%
14	58%
15	73%
16	35%
17	25%
18	67%

The compounds or formulations employed in the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the cas

of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The formulations employed in the present invention normally will consist of at least one compound of Formula I mixed with a carrier, or diluted by a carrier,or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethan , dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and

binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention are capsules, tablets, suppositories, and injectable solutions. Especially preferred are formulations for oral ingestion.

Example 19

Preparation of Membrane Vesicles

HL60/ADR cells (human leukemia cells grown in adriamycin and overexpressing MRP), revertant HL60 cells, and parental HL60 cells, respectively, were harvested by centrifugation after cultivation in cell culture and plasma membrane vesicles were prepared according to standard methods. Briefly, the cells were lysed by incubation in hypotonic buffer (0.5 mM sodium phosphate (pH 7.0), 0.1 mM EDTA supplemented with protease inhibitors) for 1.5 hours, followed by homogenization in a homogenizer. After centrifugation of the homogenate at 12,000 x g(4°C, 10 minutes), the supernatant was centrifuged at 100,000 x g at 4°C for 45 minutes. The resulting pellet was homogenized in incubation buffer (250 mM sucrose-10 mM tris-HCl, pH 7.4) and layered over 38% sucrose in 5 mM 4(2-hydroxyethyl)-1-piperazineethanesulfonic acid/KOH, pH 7.4. After centrifugation at 280,000 x g at 4°C for 2 hours, the interphase was collected, washed by centrifugation in incubation buffer (100,000 x g) and passed 20 times through a 27-gauge needle. The resulting membrane vesicles had enriched plasma membranes with moderate contaminations from endoplasmic reticulum and Golgi's apparatus.

Example 20

ATP-Dependent Transport

The ATP-dependent transport of [^{3}H]LTC_4 and S-(2,4-dinitrophenyl) [^{3}H]glutathione into membrane vesicles was measured by rapid filtration. Membrane vesicles (50 µg of protein) were incubated in the presence of 4 mM ATP, 10 mM $MgCl_2$, 10 mM of creatine phosphate, and the labeled substrate in an incubation buffer containing 250 mM sucrose and 10 mM Tris-HCl, pH 7.4. The final volume was 110 µl. Aliquots of 20 µl were taken at predetermined times and diluted in 1 ml of ice-cold incubation buffer. The dilute samples were filtered immediately through a nitrocellulose membrane (0.2 µm pore size), presoaked in incubation buffer using a rapid filtration device and rinsed twice with 5 ml of incubation buffer. The filters were immersed in liquid and measured in a liquid scintillation counter. ATP was replaced by an equal concentration of 5'-AMP in a control experiment. All rates of the ATP-dependent transport were obtained by subtracting the values obtained in the presence of 5'-AMP from those measured in the presence of ATP.

The active ATP-dependent transport of [^{3}H]LTC_4, which took place into the fraction of the "inside out"-oriented vesicles, was investigated during a 3-minute period (Figure 1). Using vesicles from the parental as well as the revertant cells, which both exhibited a low MRP expression, the rate of the ATP-dependent transport of [^{3}H]LTC_4 at the standard concentration of 50 nM was below 1 pmol x mg protein^{-1} x min^{-1}. The HL60/ADR cells, which overexpressed MRP, showed rapid ATP dependent transport of LTC_4 (50 nM) at an initial transport rate of 25 $\pm$ 2 pmol x mg protein^{-1} x min^{-1} (Figure 1). The amount of [^{3}H]LTC_4 taken up by the vesicles was markedly decreased by the growing osmolarity of the extravesicular medium. Thus [^{3}H]LTC_4 was transported into the intravesicular space.

The right-hand portion of Figure 1 shows that the ATP-dependent transport of S-(2,4-dinitrophenyl-[^{3}H]glutathione at a concentration of 5 µM using HL60/ADR membranes was 50 ± 4 pmol x mg protein^{-1} x min^{-1}. The transport rate of the revertant and parental HL60 cells was 10 times less. Figure 4 further reveals that the receptor antagonist MK 571 is a potent inhibitor of the ATP-dependent LTC_4 transport.

Example 21

Photoaffinity Labeling

Vesicle suspensions (200 µg protein) were incubated with 74 kBq [^{3}H]LTC_4 (150 nM) at 37°C for 10 minutes, shock-frozen in liquid nitrogen and irradiated at 300 nm for 5 minutes. For the purpose of competition studies, the vesicle preparations were preincubated with 50 µM of MK 571 at 4°C for 30 minutes. The photoaffinity labeling with 370 kBq of 8-azido-[α-^{32}P]ATP (10 µM) was carried out in a similar way as described above, with incubation at 4°C for 2 minutes and irradiation at 350 nm for 10 minutes.

LTC_4-binding membrane proteins were detected by direct photoaffinity labeling using [^{3}H]LTC_4 as a photolabile ligand. A marked difference in the [^{3}H]LTC_4 labeling pattern of the membranes from the different cell lines was observed at a molecular weight of 190 kDa (Figure 2). In the HL60/ADR membranes, a predominant 190 kDa protein was labeled (Figure 2, Panel A), whereas in the membranes from the revertant and parental cells only a slight labeling was detected in this range (Figure 2, Panels B and C). The [^{3}H]LTC_4 labeling of the 190 kDa protein was competitively suppressed by the transport-inhibitor MK 571 (Figure 2, Panel A). Another significantly labeled protein of 110 kDa was observed in the membranes from all three cell lines.

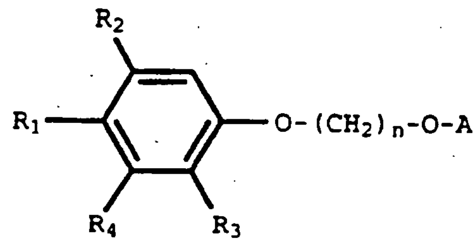
The photoaffinity labeling using 8-azido-[^{32}P]ATP also showed a strongly labeled band of a 190 kDa protein in the

membranes of HL60/ADR cells but not in the revertant or parental cell membranes (Figure 3).

A series of experiments utilizing [^{3}H]etoposide and [^{3}H]etoposide glucuronide were performed in substantial accordance with the method of Example 20. The results of this series of experiments unequivocably demonstrates MRP -mediated, ATP-dependent transport of conjugated cytostatic drugs in membrane vesicles of MRP-overexpressing drug-resistant human tumor cells by direct transport measurements. Reference to the Figures illustrates: the ATP-dependent transport of the etoposide glucuronide is mediated by MRP; the unconjugated etoposide is not a substrate for MRP; and MRP-mediated ATP-dependent transport of the etoposide glucuronide is competitively inhibited by MK 571 at a 5 μM concentration.

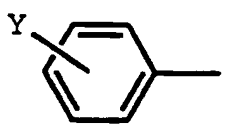
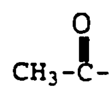
We claim:

1. Use of a compound having the formula



I

wherein

R_1 is  or 

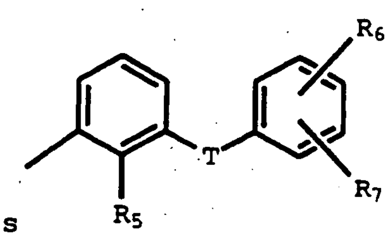
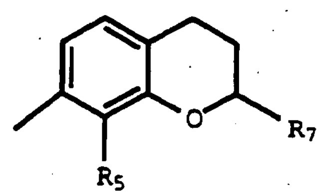
Y is hydrogen or halo;

R_2 is hydrogen, -OH, or $-OCH_3$;

R_3 is C_1-C_6 alkyl;

R_4 is hydrogen, -OH, or $-OCH_3$;

n is 3, 4, or 5;

and A is  or  ;

where

R_5 is hydrogen, C_1-C_6 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, or phenyl;

R_6 is hydrogen or halo;

R_7 is -COOH or 5-tetrazolyl;

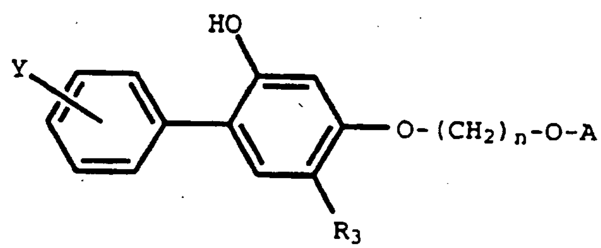
T is a bond, $-CH_2-$, -O-, -C(=O)-, or $-S(O)_q-$; and

q is 0, 1, or 2;

provided when one of R_2 and R_4 is -OH or $-OCH_3$, the other of R_2 and R_4 must be hydrogen,

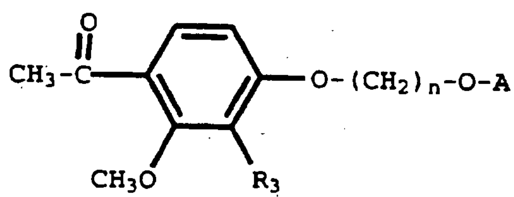
or a pharmaceutically acceptable base addition salt or solvate thereof for the manufacture of a medicament for use in the treatment of cancer.

2. The use of Claim 1 employing a compound of the structure



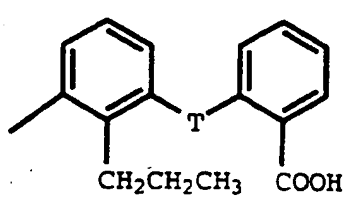
or a pharmaceutically acceptable base addition salt or solvate thereof.

3. The use of Claim 1 employing a compound of the structure



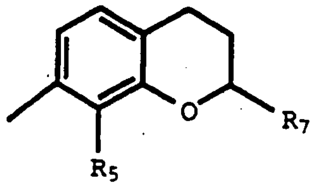
or a pharmaceutically acceptable base addition salt or solvate thereof.

4. The use of Claim 1 employing a compound wherein A is



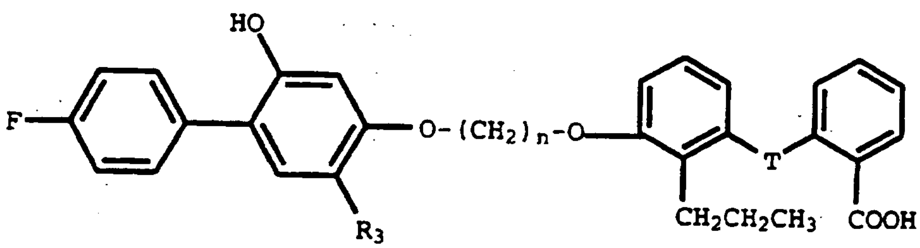
or a pharmaceutically acceptable base addition salt or solvate thereof.

5. The use of Claim 1 employing a compound wherein A is



or a pharmaceutically acceptable base addition salt or solvate thereof.

6. The use of Claim 1 employing a compound of the structure



or a pharmaceutically acceptable base addition salt or solvate thereof.

7. The use of Claim 6 employing the compound 2-[[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]propoxy]phenyl]methyl]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

8. The use of Claim 6 employing the compound 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]thiophenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

9. The use of Claim 6 employing the compound 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]propoxy]benzoyl]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

10. The use of Claim 3 employing the compound 8-propyl-7-[3-[4-acetyl-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

11. The use of Claim 6 employing the compound 2-[2-propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]butoxy]phenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

12. The use of Claim 2 employing the compound 2-[2-(phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

13. Use of amphiphilic anions having a molecular weight of 300 to 950 (daltons) for inhibiting the membrane transport mediated by the "multidrug resistance-associated protein" (MRP protein).

14. Use according to claim 13, characterized in that the amphiphilic anions are conjugates of lipophilic compounds having anionic groups selected from carboxyl, glucuronic acid, glutathione S, sulfate and cysteinylglycine groups.

15. Use according to Claim 13 or 14, characterized in that substances structurally related to the leukotrienes C4, D4, and E4, respectively, are used as inhibitors of the MRP protein.

16. Use according to any one of Claims 13 to 16, characterized in that cysteinyl-leukotriene receptor antagonists and compounds structurally related thereto are used as inhibitors of the MRP protein.

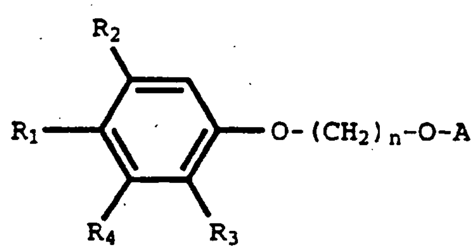
17. Use according to any one of Claims 13 to 17, characterized in that the inhibitor is employed in a concentration of 0.5 to 50 mg/kg body weight of the patient.

18. Use according to any one of Claims 13 to 17, characterized in that the concentration of the inhibitor is 0.1 to 10 micromolar at the site of action.

19. Test kit for measuring the inhibition of the MRP protein, containing membrane vesicles, ATP and radioactively labeled leukotrienes C_4, D_4 and/or E_4 or fluorescent structural analogs of leukotriene C_4, D_4 and/or E_4

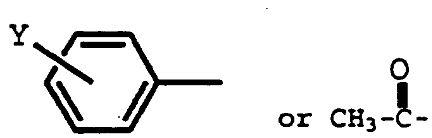
20. A method of reversing MRP-mediated multiple drug resistance comprising administering an effective amount of a MRP reversal agent.

21. A method of reversing MRP-mediated multiple drug resistance comprising administering an effective amount of a compound of the formula:



I

wherein

R_1 is 

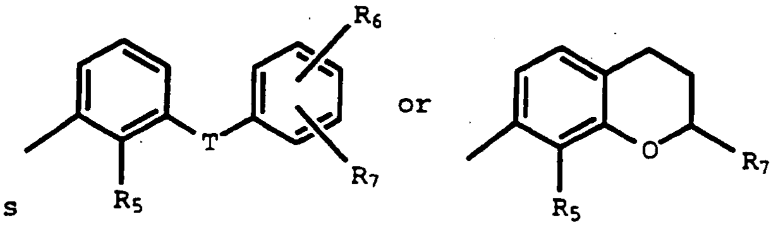
Y is hydrogen or halo;

R_2 is hydrogen, -OH, or $-OCH_3$;

R_3 is C_1-C_6 alkyl;

R_4 is hydrogen, -OH, or $-OCH_3$;

n is 3, 4, or 5;

and A is  ;

where

R_5 is hydrogen, C_1-C_6 alkyl, C_2-C_5 alkenyl, C_2-C_5 alkynyl, benzyl, or phenyl;

R_6 is hydrogen or halo;

R_7 is -COOH or 5-tetrazolyl;

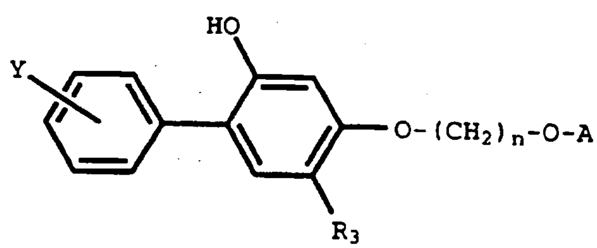
T is a bond, $-CH_2-$, -O-, -C(=O)-, or $-S(O)_q-$; and

q is 0, 1, or 2;

provided when one of R_2 and R_4 is -OH or $-OCH_3$, the other of R_2 and R_4 must be hydrogen,

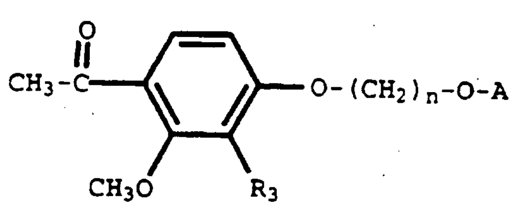
or a pharmaceutically acceptable base addition salt or solvate thereof.

22. The method of Claim 21 employing a compound of the structure



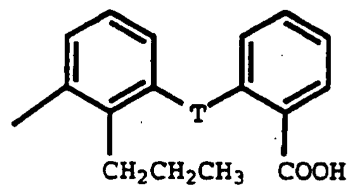
or a pharmaceutically acceptable base addition salt or solvate thereof.

23. The method of Claim 1 employing a compound of the structure

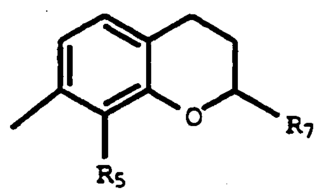


or a pharmaceutically acceptable base addition salt or solvate thereof.

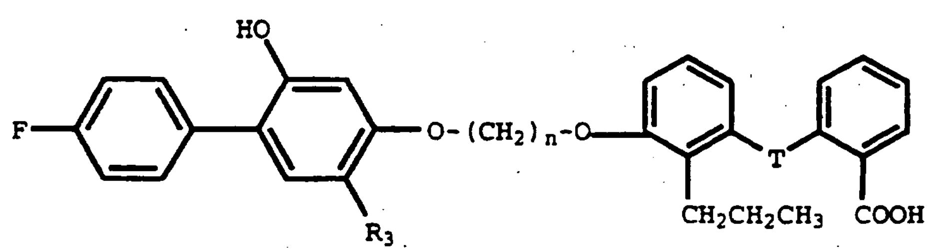
24. The method of Claim 21 employing a compound

wherein A is  or a pharmaceutically acceptable base addition salt or solvate thereof.

25. The method of Claim 21 employing a compound

wherein A is  or a pharmaceutically acceptable base addition salt or solvate thereof.

26. The method of Claim 21 employing a compound of the structure



or a pharmaceutically acceptable base addition salt or solvate thereof.

27. The method of Claim 25 employing the compound 2-[[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]propoxy]phenyl]methyl]benzoic acid or a

pharmaceutically acceptable base addition salt or solvate thereof.

28. The method of Claim 25 employing the compound 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxy-phenoxy]propoxy]thiophenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

29. The method of Claim 25 employing the compound 2-[2-propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]propoxy]benzoyl]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.
30. The use of Claim 24 employing the compound 8-propyl-7-[3-[4-acetyl-3-methoxy-2-propylphenoxy]propoxy]-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

30. The method of Claim 25 employing the compound 2-[2-propyl-3-[4-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)-phenoxy]butoxy]phenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

31. The method of Claim 22 employing the compound 2-[2-(phenylmethyl)-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable base addition salt or solvate thereof.

32. A process for identifying compounds which reverse MRP-mediated multiple drug resistance comprising evaluating a test compound for its ability to diminish MRP-mediated transport of leukotrienes or structural analogs thereof.

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Figure 1

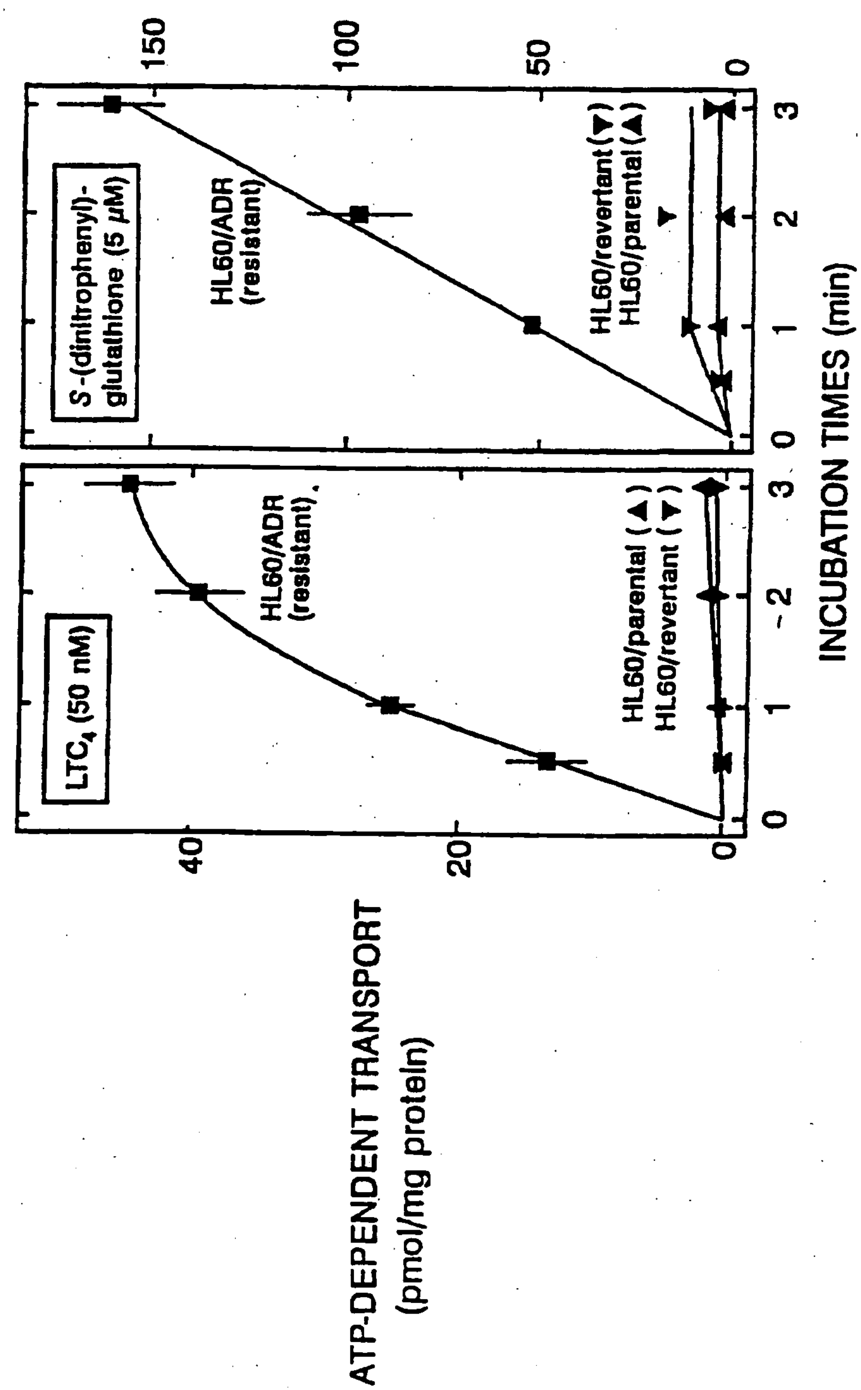
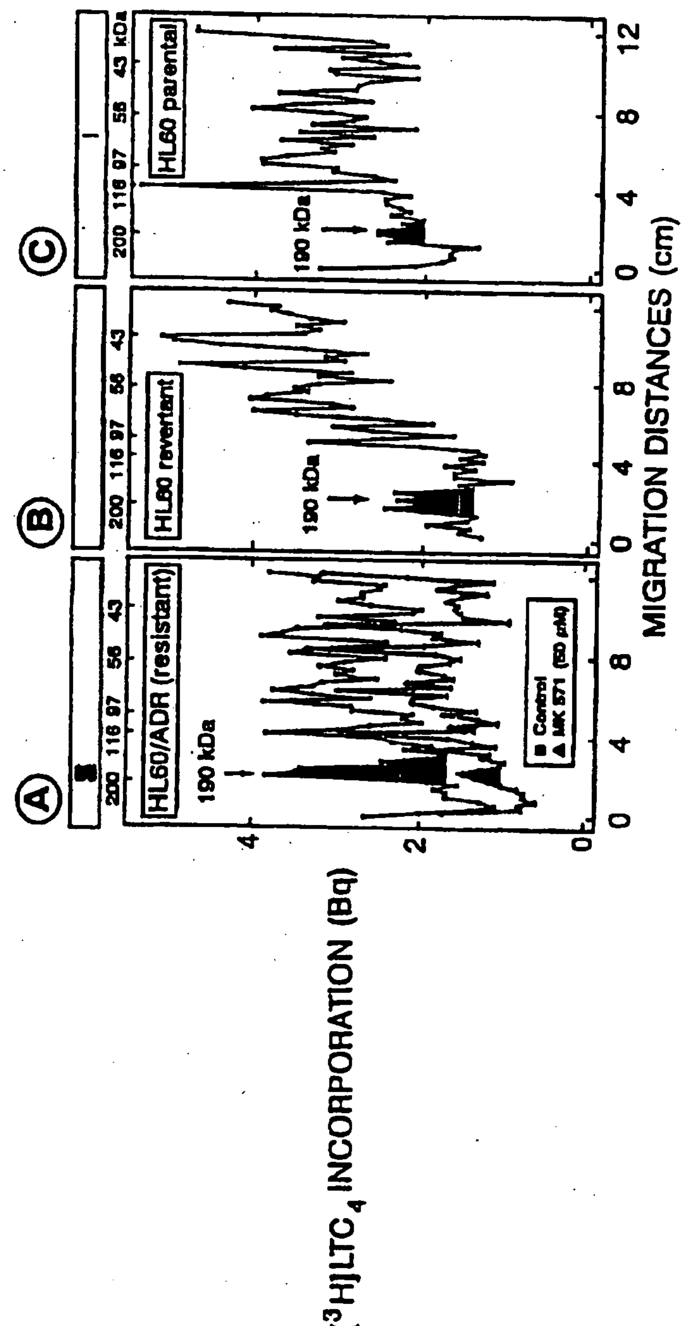

S-(dinitrophenyl)-glutathione (5 μM)
HL60/ADR (resistant)
HL60/revertant (▼)
HL60/parental (▲)
150
100
50
0
LTC4 (50 nM)
HL60/ADR (resistant)
HL60/parental (▲)
HL60/revertant (▼)
40
20
0
0
1
2
3
INCUBATION TIMES (min)
ATP-DEPENDENT TRANSPORT (pmol/mg protein)

Figure 2


A
B
C
HL60/ADR (resistant)
HL60 revertant
HL60 parental
200 116 97 58 43
200 116 97 58 43
200 116 97 58 43 kDa
190 kDa
190 kDa
190 kDa
■ Control
▲ MK 571 (50 μM)
0 4 8 0 4 8 0 4 8 12
MIGRATION DISTANCES (cm)
0 2 4
[3H]LTC4 INCORPORATION (Bq)

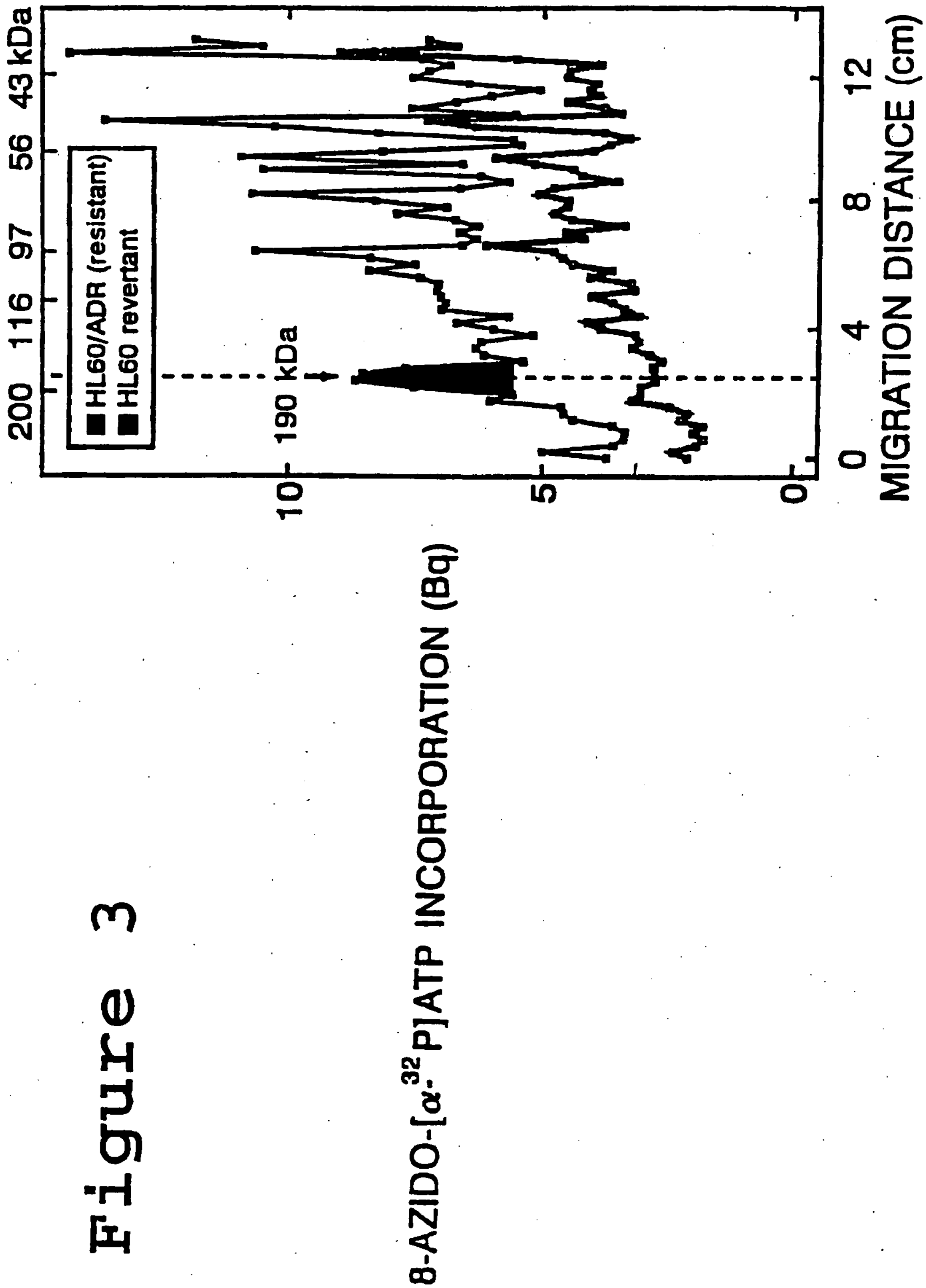
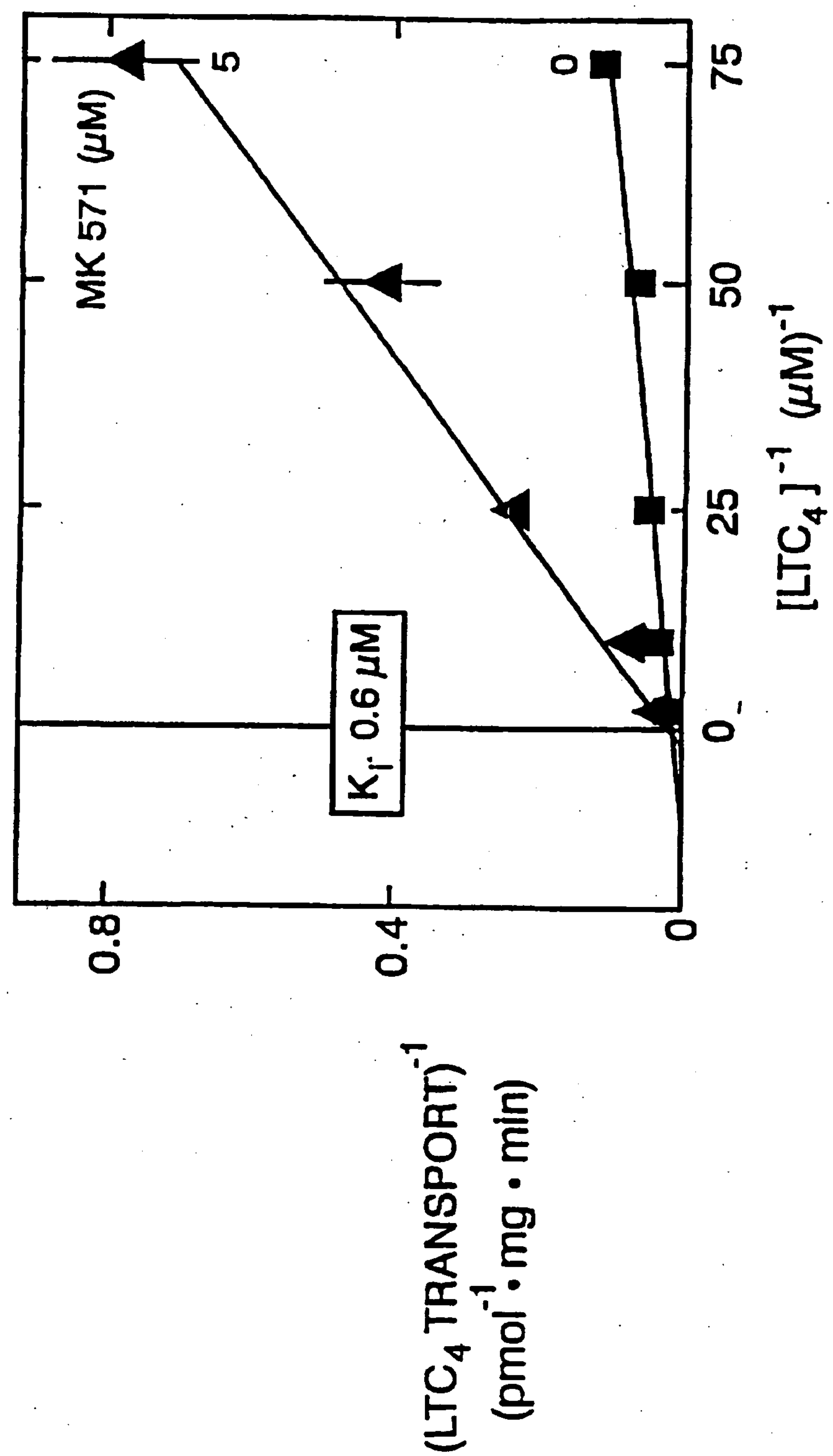

200
116
97
56
43 kDa
HL60/ADR (resistant)
HL60 revertant
190 kDa
10
5
0
0
4
8
12
MIGRATION DISTANCE (cm)
8-AZIDO-[α-32P]ATP INCORPORATION (Bq)

Figure 3

Figure 4


MK 571 (μM)
5
0
K$_i$: 0.6 μM
0.8
0.4
0
0
25
50
75
$[LTC_4]^{-1}$ $(\mu M)^{-1}$
$(LTC_4\ TRANSPORT)^{-1}$
$(pmol^{-1} \cdot mg \cdot min)$

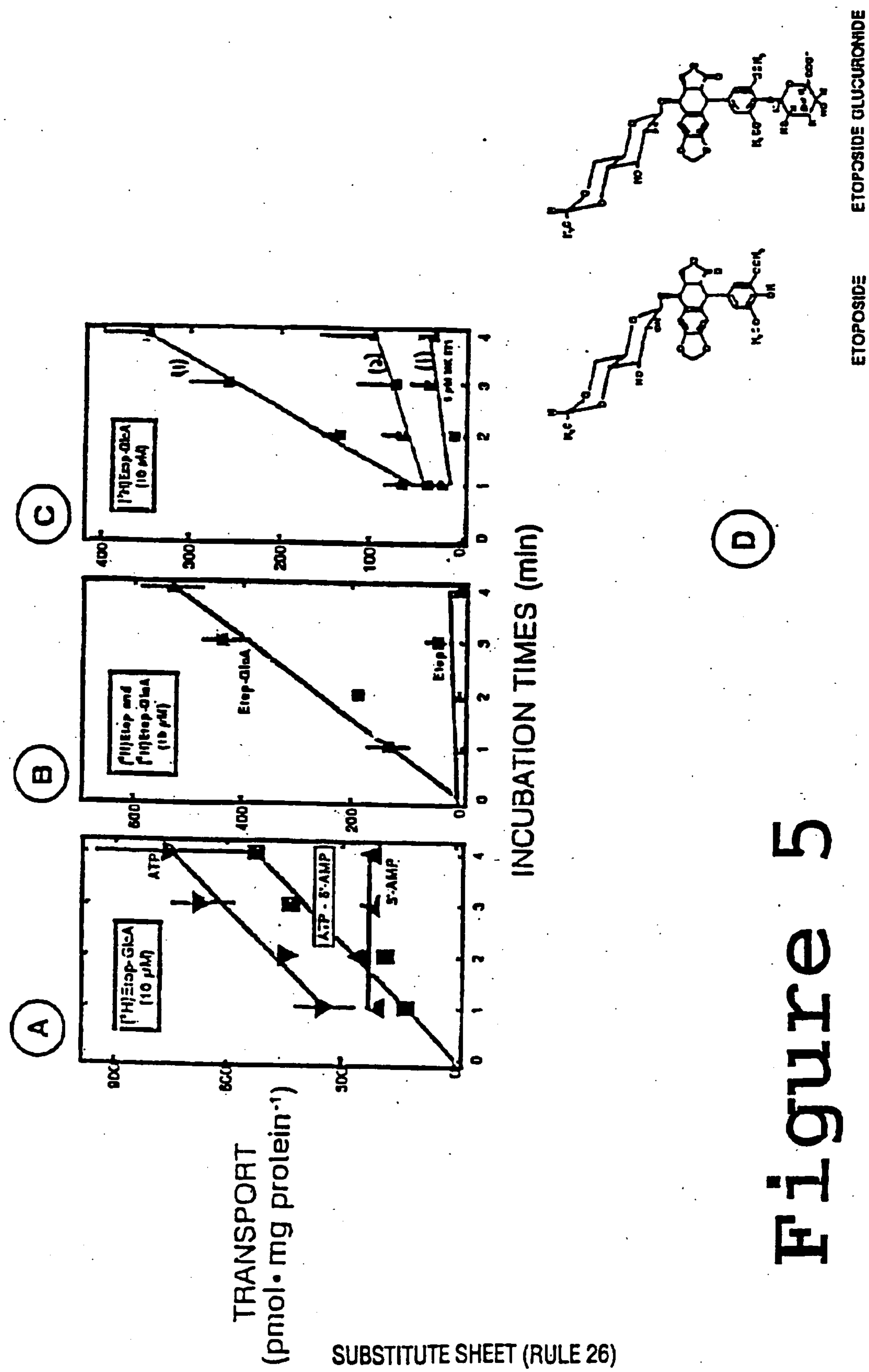
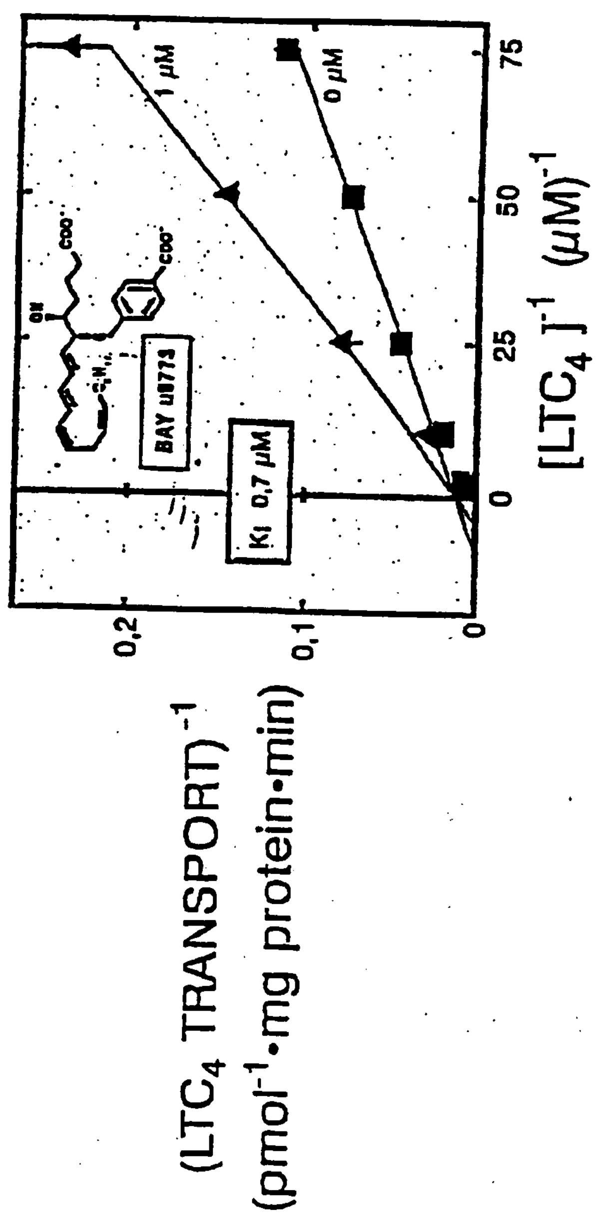

A
B
C
D
TRANSPORT
(pmol • mg protein-1)
INCUBATION TIMES (min)
ATP
ATP - 5'-AMP
5'-AMP
Etop-GlcA
Etop
ETOPOSIDE
ETOPOSIDE GLUCURONIDE

Figure 5

Figure 6


(LTC4 TRANSPORT)-1
(pmol-1·mg protein·min)
0,2
0,1
0
0
25
50
75
[LTC4]-1 (μM)-1
1 μM
0 μM
BAY u9773
Ki 0,7 μM

PCT

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International Bureau

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(63) Related by Continuation
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Filed on 31 August 1994 (31.08.94)

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(54) Title: METHODS FOR IDENTIFYING AND TREATING RESISTANT TUMORS

(57) Abstract

This invention provides a method of identifying and reversing multidrug resistance in a multidrug resistance tumor comprising administering a multidrug resistance reversing amount of any of the compounds as defined herein.

FOR THE PURPOSES OF INFORMATION ONLY

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/11125

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/19 A61K31/41 A61K31/35 A61K31/195
A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 596 725 (ELI LILLY AND COMPANY) 11 May 1994 see column 4, line 5 - line 9; claims 4,10 ---	1-12, 20-31
X,P	EP,A,0 652 004 (ELI LILLY AND COMPANY) 10 May 1995 see page 4, line 26 - line 35 ---	1-12, 20-31
X	CHEMICAL ABSTRACTS, vol. 114, no. 9, 4 March 1991 Columbus, Ohio, US; abstract no. 81260g, XP002004827 see abstract & JP,A,02 218 654 (ONO PHARMACEUTICAL CO., LTD.) 31 August 1990 --- -/--	1-12, 20-31

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
5 June 1996	14.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Theuns, H

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	ADVANCES IN ENZYME REGULATION, vol. 27, 1988, pages 287-294, XP002004819 L.P.WENNOGLE ET AL.: "profiling of inhibitors of protein kinase c" see page 287	1-12, 20-31
Y	J.PHARMACOL.EXP.THER., vol. 260, no. 1, January 1992, pages 187-191, XP002004820 D.VILLANI-PRICE ET AL.: "Multiple Actions of the Leukotriene B4 Receptor Antagonist SC-41930" see abstract	1-12, 20-31
Y	BIOCHIM.BIOPHYS.ACTA LIPIDS LIPID METAB., vol. 1168, no. 1, 1993, pages 23-29, XP002004821 M.MORI ET AL.: "Energy-dependent export of leukotriene B4 in Xenopus oocytes" see abstract	1-12, 20-31
Y	AGENTS ACTIONS, vol. 32, no. 3-4, March 1991, pages 339-342, XP002004822 L.KEMÉNY ET AL.: "SC-41930, a leukotriene B4 receptor antagonist, inhibits 12(S)-hydroxyeicosatetraenoic acid (12(S)-HETE) binding to epidermal cells" see abstract	1-12, 20-31
A	EP,A,0 544 488 (ELI LILLY AND COMPANY) 2 June 1993 cited in the application see column 2	1-12, 20-31
A	EP,A,0 292 977 (G.D.SEARLE & CO.) 30 November 1988 cited in the application see page 4	1-12, 20-31
A	US,A,5 324 743 (ELI LILLY AND COMPANY) 28 June 1994 cited in the application see column 1	1-12, 20-31
X	EUR.J.BIOCHEM., vol. 220, no. 2, 1 March 1994, pages 599-606, XP000570964 I.LEIER ET AL.: "Characterization of the ATP-dependent leukotriene C4 export carrier in mastocytoma cells" see the whole document	13-19,32

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FEBS LETT., vol. 279, no. 1, 11 February 1991, pages 83-86, XP000570335 T SCHAUB ET AL.: "ATP-dependent leukotriene export from mastocytoma cells" see the whole document ---	13-19,32
X,P	J.BIOL.CHEM., vol. 269, no. 45, 11 November 1994, pages 27807-27810, XP002004823 I.LEIER ET AL.: "The MRP Gene Encodes an ATP-dependent Export Pump for Leukotriene C4 ans Structurally Related Conjugates" see the whole document ---	13-19,32
X,P	ANTICANCER DRUGS, vol. 5, no. suppl. 1, September 1994, page 4 XP000570353 G.JEDLITSCHKY ET AL.: "ATP-dependent glutathione conjugate transport in HL60 cells overexpressing the multidrug resistance associated protein (MRP)" see abstract ---	13-19,32
T	CANCER RESEARCH, vol. 56, no. 5, 1 March 1996, pages 988-994, XP002004824 G.JEDLITSCHKY ET AL.: "Transport of Glutathione, Glucuronate, and Sulfate Conjugates by the MRP Gene-encoded Conjugate Export Pump" see the whole document ---	13-19,32
T	BIOCHEM.J., vol. 314, no. 2, 1 March 1996, pages 433-437, XP000570352 I.LEIER ET AL.: "ATP-dependent glutathione disulphide transport mediated by the MRP gene-encoded conjugate export pump" see abstract ---	13-19,32
X,P	PROC.NATL.ACAD.SCI. USA, vol. 91, December 1994, pages 13033-13037, XP002004825 M.MÜLLER ET AL.: "Overexpression of the gene encoding the multidrug resistance-associated protein results in increased ATP-dependent glutathione S-conjugate transport" see the whole document ---	13-19,32

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2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	CURRENT OPINION IN ONCOLOGY, vol. 7, no. 6, November 1995, pages 532-540, XP000570351 H.J.BROXTERMAN ET AL.: "Multidrug resistance proteins and other drug transport-related resistance to natural product agents" see the whole document ---	13-19,32
X,P	BIOCHEM.BIOPHYS.RES.COMMUN., vol. 208, no. 1, 8 March 1995, pages 345-352, XP002004826 V.GEKELER ET AL.: "THE LEUKOTRIENE LTD4 RECEPTOR ANTAGONIST MK571 SPECIFICALLY MODULATES MRP ASSOCIATED MULTIDRUG RESISTANCE" see the whole document -----	13-19,32

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13-18, 20-31 are directed to a method of treatment of the human/animal body the search will be based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please see annex.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See continuation sheets

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Claims 1-12, 21-31 and 13-18, respectively:
Rule 13.1-2 PCT requires that claimed alternatives are of a similar nature in having a common property or activity, and either a significant structural element shared by all of the alternatives, or in case a common structure is absent, all alternatives belonging to a recognized class of chemical compounds in the art to which the invention pertains [compare "Administrative Instructions under the PCT", Annex B, Unity of Invention, paragraph (f)].

The compounds specified in claims 1-12, 21-31 and 13-18, respectively, do share a common property or activity, in inhibiting the function of MRP, but do not share a significant structural element and each different group represents a distinct recognized class of chemical compounds in the pharmaceutical art to which the invention pertains.

In identifying agents which inhibit the function of MRP the man skilled in the art could have found compounds belonging to a single family of mutually structurally closely related products, representing a single (unitary) solution. In the present case, however, the skilled man has selected at least two structurally substantially different groups of compounds, representing independent alternative solutions, each characterised by its own special technical feature (the specific structural features of the compounds to be used).

Claim 20:
The subject matter of claim 20 relates to a structurally not further specified "MRP reversal agent". As such, this claim is to be included in the first invention specified in the claims.

Claims 19 and 32, respectively:
The subject matter of claim 32, a process for identifying compounds which reverse MRP-mediated MDR, and the subject matter of claim 19, a test kit for measuring the inhibition of MRP, represent mere alternatives for the method for determining the ability of an agent to bind to MRP, disclosed in claim 4 of EP-A-0596725. Both claims relate in an aspect to leukotrienes. The subject matter of these claims therefore is to be included in the invention of claims 13-18.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed in the communication pursuant to Article 17(3)(a) PCT. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
Searching these different subjects would have caused major additional searching efforts.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

YES 1. Claims 1-12, 20-31: Use of compounds of formula I for the manufacture of a medicament for use in the treatment of cancer, and a method for reversing MRP-mediated MDR.

YES 2. Claims 13-19, 32: Use of amphiphilic anions having a molecular weight of 300 to 950 (daltons) for inhibiting the membrane transport mediated by MRP, a test kit for measuring the inhibition of MRP, and a process for identifying compounds which reverse MRP-mediated MDR [as far as the subject matter of these claims is not comprised in subject 1].

Rule 13.1 PCT deals with the requirement of unity of invention and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept. Rule 13.2 PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.

The problem underlying the present application is to provide a means for reversing multiple drug resistance (MDR) linked to MRP.
The proposed solution (as defined in the claims) relates to the use of compounds of formula I for the manufacture of a medicament for use in the treatment of cancer, the use of amphiphilic anions having a molecular weight of 300 to 950 (daltons) for inhibiting the membrane transport mediated by MRP, a test kit for measuring the inhibition of MRP, a method for reversing MRP-mediated MDR, and a process for identifying compounds which reverse MRP-mediated MDR.

According to the description (page 3), the present application embraces the elucidation of the role which MRP (also known as P190) plays in MDR, which allowed the development of MRP-based assays for identifying compounds which reverse MDR by blocking the transport function of MRP.

The concept which a priori links the subject matters of the claims of the present application resides in the elucidation of the role which MRP (also known as P190) plays in MDR.

In relation to MDR EP-A-0596725 discloses a method for determining the ability of an agent to bind to MRP (claim 4) and a method for treating epipodophyllotoxin resistant neoplasms comprising the administration of an agent which inhibits MRP in conjunction or in combination with epipodophyllotoxin (claim 10). This documents also discloses that "agents which inhibit the function of P190 [MRP] offer significant clinical opportunities because by reversing the anthracycline/epipodophyllotoxin resistant phenotype they allow resumption of therapy with oncolytics of these classes of oncolytics" (column 4, lines 5-9).

The role MRP plays in MDR consequently is known in the prior art. Equally, the idea to identify and use agents which inhibit the function of MRP is not novel, and cannot serve as a single general inventive concept, linking the subject matters of the claims.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Obscurities, Inconsistencies, Contradictions, etc...
The definition of compounds by means of a functional feature like "amphiphic anions" and a molecular weight range and further variants is not sufficient for identifying these compounds. Similarly, the definition of a compound as a"MRP reversal agent" is not enabling its structural identification. A complete search is virtually impossible under these circumstances.

Claims searchable completely: 1-12,21-32
Claims searchable incompletely: 13-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/11125

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0596725	11-05-94	CA-A-	2102256	06-05-94
		JP-A-	6217790	09-08-94
EP-A-0652004	10-05-95	AU-B-	7578694	04-05-95
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